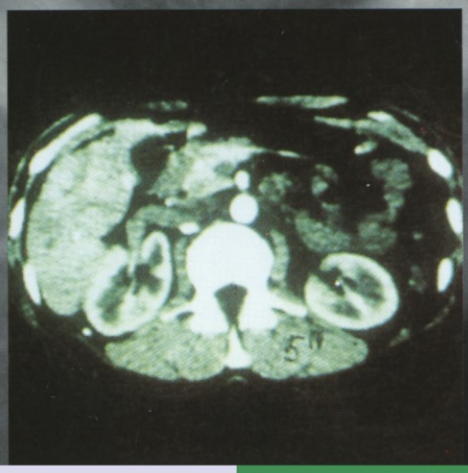

Ulrich Speck
(Editor)

Contrast Media

Overview, Use and Pharmaceutical Aspects

4th, revised Edition

Springer

ULRICH SPECK (ED.)

CONTRAST MEDIA

Overview, Use and Pharmaceutical Aspects

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Professor Dr. Ulrich Speck
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D. Herrmann, U. Hübner-Steiner, A. Lenzner, W. Mützel,
E. Post, H. Steins and V. Taenzer

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CONTRAST MEDIA IN DIAGNOSTIC IMAGING

The significance of contrast media was recognized almost simultaneously with the discovery of X-rays. Too many structures in the body remain invisible on X-ray and can only be enhanced through the use of contrast media. As a result, much effort has been made to better adapt contrast media and the techniques of their administration to diagnostic requirements and to develop better-tolerated products. At the same time, the technique continued to develop; computed tomography and subtraction techniques increase the contrast resolution of X-ray imaging. With ultrasound and magnetic resonance imaging soft tissue can be depicted much better, sometimes allowing exact identification of blood vessels which cannot be seen on non-contrast-enhanced X-ray images. The principle "contrast media," however, has proven itself well, especially in the new X-ray techniques and magnetic resonance imaging, and will also undoubtedly increase the diagnostic potential of ultrasound since these substances which are introduced from outside the body make it possible to visualize functions which otherwise could not be seen. Contrast enhancement also improves the quality of the morphological information.

Visualization of functions

- elimination (kidney, liver)
- transport processes (bloodstream, cerebrospinal fluid, intestinal contents, imaging of the liver)
- perfusion (all organs)
- permeability and barriers (blood-brain barrier, cysts)
- metabolism (MR spectroscopy)

Morphology

Creating and increasing contrasts, for example, through

- varying contrast media concentrations in individual tissues
- temporal changes of radiation absorption or signal intensities
- change in quality (frequency) of the signals by contrast media.

Although the information gained through the use of contrast media is not just restricted to the visualization of anatomical structures, the term "contrast media" has been retained.

On the whole, all imaging techniques and all products referred to as contrast media have one thing in common – they all assist in providing visual representations of information from within the body. This information may represent anatomical structures, functions, or physical-chemical conditions.

GENERAL PRINCIPLES OF X-RAY CONTRAST MEDIA

The contrast in an X-ray film is caused by the varying absorption of X-rays by the material being irradiated. This absorption is dependent on the atomic number of the atoms present in the molecules, on the concentration of these molecules and on the thickness of the irradiated slice. In the case of chest X-rays, the bones, the airiferous lungs, the heart and other tissues provide adequate natural contrast. In other cases, however – e.g. in the abdomen –, the composition of the organs is so similar that the differences in absorption are too small; they are radiographically anonymous and must be made visible by additional measures (fig. 1).

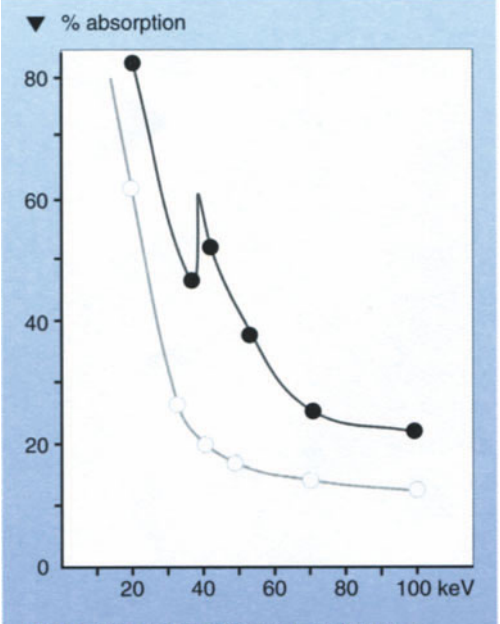


Fig. 1. Absorption of X-rays in % by water (~ soft tissue, ○–○) and an aqueous CM solution with 20 mg iodine/ml (●–●) with slice thickness of 1 cm in relation to the energy of the X-rays (50 keV are achieved at about 100 kV tube voltage)

The introduction of substances of very low density (gases) into organs or surrounding structures reduces the absorption; such substances are called negative contrast media (CM). Substances with a high X-ray density contain atoms of a higher atomic number (barium or iodine). Such preparations increase the absorption of X-rays in the body and are, therefore, known as positive CM (table 1).

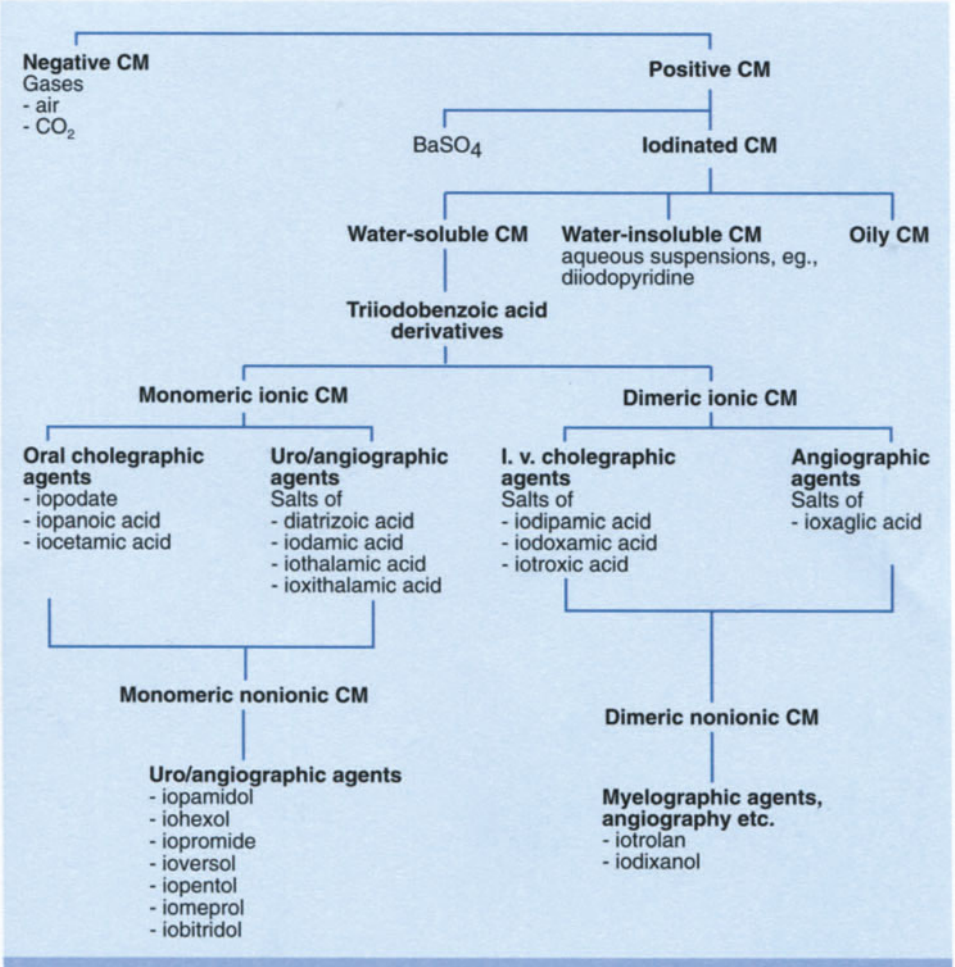


Table 1. Classification of X-ray contrast media (CM)

STRUCTURE AND PROPERTIES OF X-RAY CONTRAST MEDIA

Optimal use of CM in radiology requires a knowledge of the nature and relevant properties of the available substances. This chapter describes the properties of current and newly developed contrast-giving substances which have an influence on their behavior in the organism, their side effects and their practical utility.

The main CM in use today are insoluble barium sulfate for the diagnosis of the GI tract and water-soluble CM for the radiological demonstration of the different vascular systems, body cavities and organs.

BARIUM SULFATE

Barium is employed in the form of the insoluble sulfate for the diagnosis of the GI tract. If perforation is suspected, however, a water-soluble, iodinated CM (Gastrografin, Ultravist-370, Isovist 300) must always be chosen, since the body is virtually incapable of eliminating barium sulfate once it has entered the peritoneum. Barium sulfate is available either as a powder to be made up freshly before use or as a ready-to-use suspension. For double-contrast demonstration (filling of the lumen with gas, coating of the wall with barium sulfate), barium sulfate is either mixed with a carbon dioxide additive or a gas-forming agent is taken in addition. Common to all barium preparations is the concentration of about 1 g/ml barium sulfate or somewhat less for bowel studies. High-density preparations with a barium sulfate content of 2.5 g/ml are tailored to the special requirements of the double-contrast method [1].

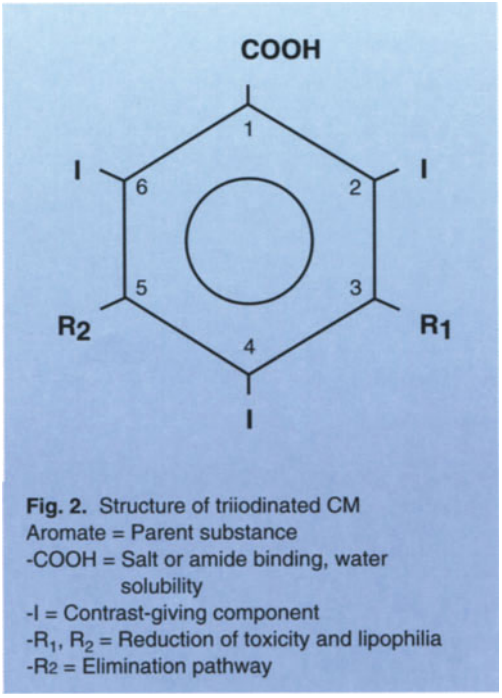


Fig. 2. Structure of triiodinated CM
Aromate = Parent substance
-COOH = Salt or amide binding, water solubility
-I = Contrast-giving component
-R_1, R_2 = Reduction of toxicity and lipophilia
-R2 = Elimination pathway

WATER-SOLUBLE CONTRAST MEDIA

The first CM on the basis of triiodobenzene were introduced in about 1950 (fig. 2) and had virtually taken over the field by the second half of the fifties. The reasons why such a homogeneous substance class still dominates a number of uses without any recognizable competition are as follows:

- Iodine is the only chemical element which combines three properties essential for the production of CM: high contrast density, chemical behavior which allows firm binding to the highly variable benzene molecule, and low toxicity.

- The iodine is optimally bound in the symmetrically substituted triiodobenzene; at 84%, the iodine content of the basic molecule is extremely high.

- Positions 1, 3 and 5 in the molecule are available to the chemist for the most diverse modifications of the physicochemical and biological properties by the introduction of side chains.

Chemical structure, biological behavior and use

The substance types shown in figure 3 were produced by varying the basic molecule of triiodobenzene. Thanks to the large number of synthesized substances, the relationship between the chemical structure and the principal biological behavior of molecules is well documented.

Conventional, highly hypertonic contrast media in uro/angiography and CT

Diatrizoic acid, which was introduced in 1953, is contained in numerous products and was the most widely used CM in the world for urography, angiography and CT for three decades.

Because its COOH group is connected directly to the triiodobenzene ring, diatrizoic acid (Urografin, Angiografin, Urovist, Urovison) is a strong acid, forming salts which are readily soluble in water. The two side chains ($-NHCOCH_3$) further improve the solubility, reduce protein binding (thereby increasing its ability to be filtered in the glomerulus) and improve above all the tolerance. The substance is eliminated almost exclusively via the kidneys.

There is a series of related compounds which are derived from diatrizoic acid; meanwhile, however, these are less important (fig. 4).

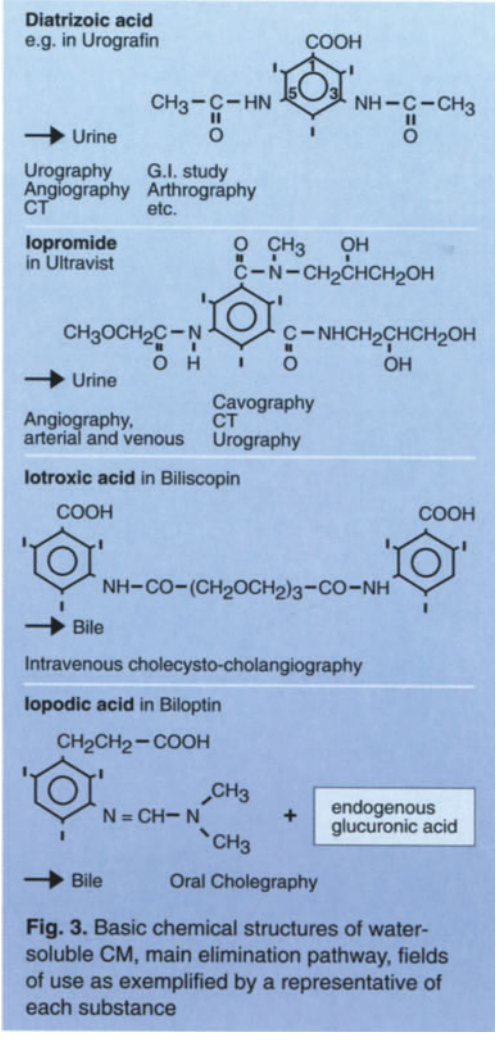


Fig. 3. Basic chemical structures of water-soluble CM, main elimination pathway, fields of use as exemplified by a representative of each substance

Low-osmolar contrast media, especially nonionic substances

In the course of the sixties, it became increasingly clear that many of the side effects of the conventional CM – particularly of those used in angiography – were caused more by the high osmolality of the concentrated CM solutions than by chemotoxicity. CM with less osmotic activity were synthesized following the basic work by Almén [2].

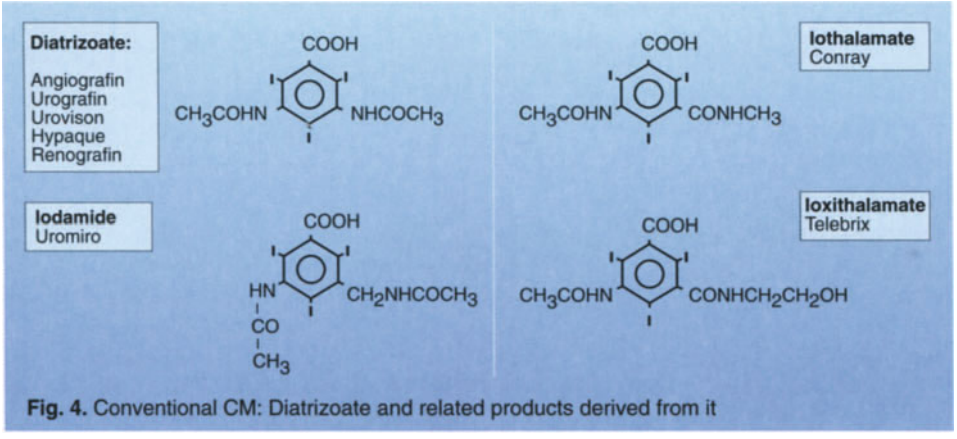


Fig. 4. Conventional CM: Diatrizoate and related products derived from it

Nonionic contrast media (figs. 5, 6). Above and beyond their reduced osmolality, nonionic CM have surprising advantages over ionic CM in two respects:

1. The neural tolerance of nonionic CM proved to be considerably better than that of ionic CM. As a result, the nonionic substances quickly replaced the ionic agents in myelography. The dimeric compound iotrolan merits particular mention. Iotrolan, which has been on the market since 1988 (Isovist), displays excellent neural and tissue tolerance which can be explained, inter alia, by its blood-isotonic character even at high concentrations.

2. The incidence of both general reactions, such as nausea and vomiting, and of the sometimes life-threatening, allergylike or idiosyncratic reactions, is apparently far lower under nonionic CM [3, 4, 33–35]. The replacement of ionic CM in angiography, urography and CT by nonionic products, is, by now, very advanced. However, the incidence of fatal reactions is too rare to allow statistical comparison.

The good general tolerance of nonionic CM compared to that of ionic CM and the low-osmolar compound

ioxaglate can be explained by the following main properties:

Nonionic contrast media

- contain no electrical charges,
- contain no cations, such as sodium or meglumine, and
- are considerably better shielded by hydrophilic side chains.

This results in minimal protein binding and enzyme inhibition and in reduced impairment of the function of biological membranes.

For the patient, this means substantially better general tolerance. Nausea and vomiting, urticaria, mucosal swelling, increased respiratory resistance and effects on the cardiovascular system are rarely observed with nonionic CM.

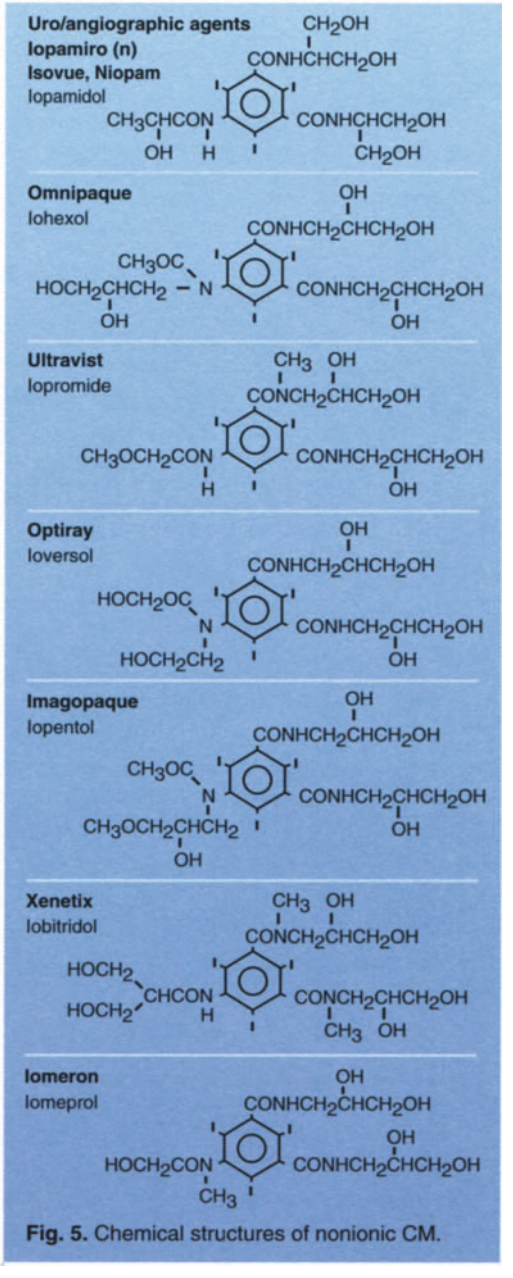


Fig. 5. Chemical structures of nonionic CM.

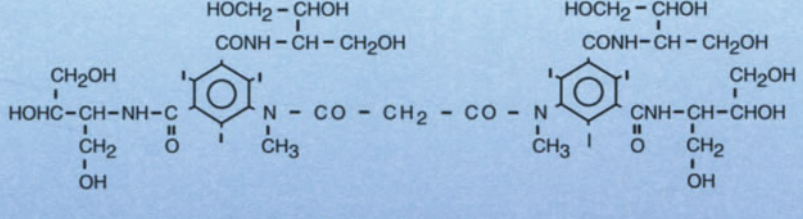
Osmolality and side effects caused by hypertonicity. Nonionic CM all have distinctly lower osmotic activities than conventional ionic CM. With the same iodine content, the osmolality at 37° C can be more than 2.5 times higher for an ionic CM than for a nonionic compound.

CM side effects caused entirely or mainly by the excessively high osmolality are:

- Vascular pain
- Endothelial damage
- Disturbance of the blood-brain barrier
- Thrombosis and thrombophlebitis
- Bradycardia in cardioangiography
- Increase of pressure in the pulmonary circulation, at least in cases of initially pathological values.

Some of these side effects occur very frequently especially in angiography with conventional CM. Wherever possible, therefore, only nonionic CM should be employed in angiography.

Myelography and other body cavities: Isovist®, Iotrolan



Angiography, urography, CT: Visipaque®, Iodixanol

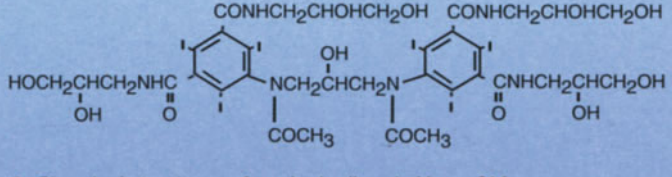


Fig. 6. Chemical structures of nonionic dimeric X-ray CM

	Osmolality (43) 300 mg I/ml, 37°C mosm/kg H_2O mean and 95% confidence interval	Viscosity, 37°C 300 mg I/ml m Pa • s	370 mg I/ml m Pa • s	Protein binding in % at 1.2 mg I/ml plasma
Iopromide	586 ± 5	4.6	9.5	0.9 ± 0.2
Iopamidol	653 ± 7	4.5	9.5	2.9 ± 0.2
Iohexol	667 ± 8	5.7	10.5*	1.5 ± 0.3
Ioversol	661 ± 3	5.5	9.0*	1.6 ± 0.9 **
Iopentol	683 ± 4	6.5	12.0*	1.9 ± 0.6 ***
Iomeprol	538	4.3	7.0*	1.7 ± 0.4
Iobitridol	695	6.0	10.0*	–

* 350 mg Iod/ml ** more than Iopromide *** less than Iohexol

Table 2. Nonionic contrast media for intravascular administration

At high dosage and irrespective of the mode of use, high osmolality CM cause general vasodilatation and a fall in blood pressure, hypervolemia and diuresis.

These effects occur to a reduced extent or only at an even higher dosage in the case of nonionic CM.

In what way do nonionic CM differ from each other?

Nonionic CM differ (because of their chemical structure) as regards their osmolality, their viscosity and their substance-specific properties. The introduction of new CM required that new comparative measurements were performed. The results of these can be found in tables 2 and 3. If account is taken of the specific properties of the individual nonionic CM when choosing which one to use, radiodiagnosis can be optimized and the risk of the examinations for the patient reduced.

	Osmolality mosm/kg H_2O	Viscosity m Pa • s, 37°C
Iotrolan		
Isovist-240	270	3.9
Isovist-300	291	8.1
Iopamidol-200	413	2.0
Iopamidol-250	580	3.0
Iohexol-180	390	2.0
Iohexol-240	520	3.3

Table 3. Nonionic contrast media for myelography and other body cavities (Isovist)

Ionic contrast media

It is also possible to produce low-osmolar ionic CM. The only one of these CM to have achieved any importance in angiography is meglumine-sodium ioxaglate (Hexabrix [5]). Its use is confined to angiography because it achieves neither the neural nor the general tolerance of nonionic CM [6, 7].

Ioxaglate (Hexabrix, only one acid function) consists of two triiodobenzene rings (dimer) which are connected via a chain (fig. 7).

This doubling of the molecular weight has no influence on the basic properties of the molecules: Good solubility, renal elimination and a lack of enteral absorption suggest the same uses as for diatrizoate. The distinctly lower osmotic pressure of the solutions of sodium-meglumine ioxaglate is the reason for its virtual painlessness in peripheral angiography. High viscosity and an increased rate of general reactions are serious disadvantages of ioxaglate.

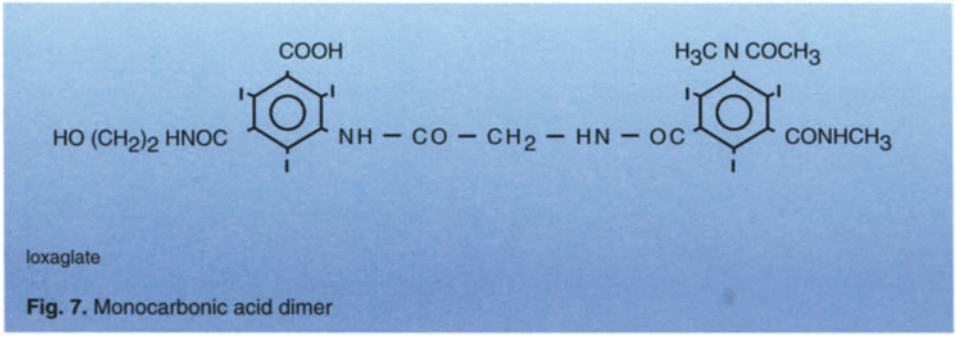


Fig. 7. Monocarbonic acid dimer

Contrast media for intravenous cholegraphy

Like in urography, in i.v. cholegraphy also there are several CM available which are chemically very similar. Unlike the urographic agents, however, not every i.v. cholegraphic agent has its specific advantages and disadvantages, since it was possible to improve the first i.v. cholegraphic agent, iodipamide, in respect of opacification and tolerance.

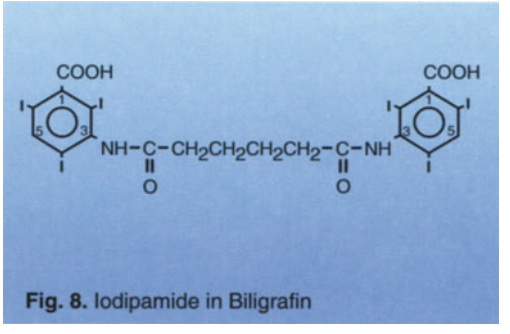


Fig. 8. Iodipamide in Biligrafin

Iodipamide (Biligrafin) is the prototype of the i.v. biliary CM. It is a dimeric diacid which contains no further side chains. It is eliminated for the greater part with the bile without the molecules undergoing any chemical changes (metabolism) (fig. 8).

The reasons are:

- The unsubstituted positions 5 and 3 lead to binding to plasma protein and, consequently, delay glomerular filtration decisively.
- The acid groups and the lipophilic properties of the molecule permit the use of the hepatic anion transport mechanism, which also causes the biliary elimination of natural acidic metabolites.
- In contrast to the monomer, the size of the molecule exceeds the molecular weight threshold required for biliary elimination [8].

The strong acid groups prevent reabsorption after biliary elimination into the duodenum.

The modern i.v. biliary CM Biliscopin is bound somewhat less firmly to albumin. The rate of elimination and the contrast density are increased; the tolerance is very much improved, particularly in the case of the infusion formulations. Since a constant infusion

rate is decisive for tolerance the use of an automatic infusion pump is recommended.

Contrast media for oral cholegraphy

A number of CM similar in respect to their chemistry, opacification, pharmacokinetics and tolerance have been developed for oral cholegraphy (iopodate, iobenzamic, iopromic, iocetamic and iopanoic acid).

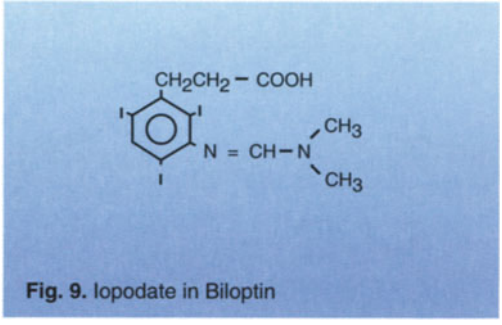


Fig. 9. Iopodate in Biloptin

Sodium iopodate (Biloptin) displays the structure typical of many oral cholegraphic agents (fig. 9):

- The acid group is bound to the benzene ring not directly, but via a chain (bridge). Oral cholegraphic agents are, therefore, very much weaker acids than the CM for intravenous use; at the pH value of the bowel contents, they are present to some extent in the lipophilic, undissociated form and can, therefore, permeate the lipoid-containing membranes of the intestinal epithelium. The water solubility of many oral cholegraphic agents is very low at pH 7 and increases only as a result of ionization in a distinctly alkaline environment.
- Position 5 is unsubstituted, i.e the contrast agents are bound to proteins just like i.v. cholegraphic agents.
- Oral biliary CM are monomers. They gain the higher molecular weight required for biliary elimination by binding to glucuronic acid.

Cations

The ionic CM for angiography, urography, CT, i.v. cholegraphy and oral cholegraphy are sufficiently soluble in water only as salts. In the case of most oral biliary CM, the formation of salt is left to the organism. Only a few oral cholegraphic agents and all the other compounds mentioned are offered as finished salts. Iodine-free bases (usually sodium or meglumine) are used to dissolve the iodinated CM acid. At present, diatrizoate is also available as a lysine salt only in Germany and ioxithalamate as an ethanolamine (mixed) salt only in France. Numerous other cations are feasible as counterions for CM acids but, so far, no cations have been found which are better than or even as good as meglumine or sodium.

The cations introduced into the body with the CM are freely mobile independently of the CM acids and are eliminated independently of the acids. As far as is known at present, the pharmacokinetics of the acids are not affected by the cations [9, 10]. Similar to the CM anion, the meglumine cation diffuses into the extracellular space with only little uptake into the cells and is eliminated almost exclusively via the kidneys. Sodium behaves the same as endogenous sodium.

Meglumine, which was originally introduced because of the better solubility of its salts, has, in general, proved to be the better tolerated cation. Disadvantages are the higher viscosity and the somewhat stronger diuretic effect.

A certain proportion of sodium in the salt mixture is essential in cardioangiography (Urografin), in which pure sodium or meglumine salts were contraindicated already before the introduction of nonionic CM.

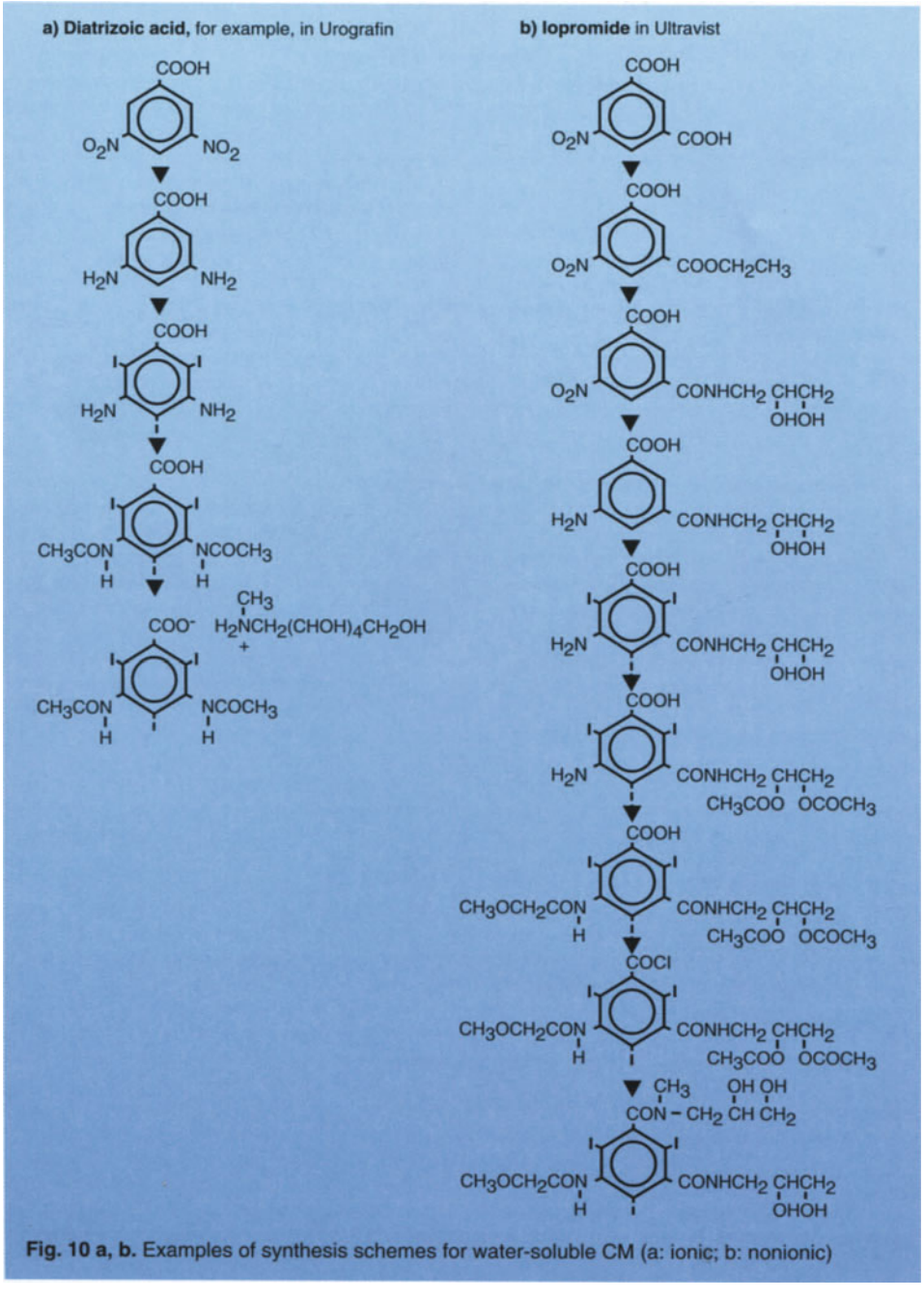


Fig. 10 a, b. Examples of synthesis schemes for water-soluble CM (a: ionic; b: nonionic)

Synthesis of water-soluble contrast media

The parent substances for the synthesis of water-soluble CM are iodine and nitrobenzoic acid derivatives. Iodine is a valuable raw material which is obtained partly from marine algae and partly from salt deposits. A significant part of the annual world production for iodine is used for the manufacture of CM.

Just what the synthesis of CM entails depends very much on the chemical structure of the compound concerned. While ionic CM can be produced from the parent substances in just a few steps (fig. 10a), the new nonionic products require a large number of steps (fig. 10b). Apart from the expenditure for materials and labor involved in each individual step, some of the material employed – including some of the usually already iodinated precursors – is also lost at each step in the synthesis. As an example, even when the yield at each individual step is 90%, the total yield of an 8-step synthesis is only 43% of the materials originally employed.

The purification of nonionic CM, which are readily soluble in water, is yet another problem. Ionic CM can be precipitated from water by acid. Nonionic agents cannot be precipitated from water but at most to a limited extent from the customary organic solvents. Consequently, the extremely high demands made on the quality of CM make the purification of nonionic substances an expensive production step because of the complicated procedures required and the high losses involved.

PHYSICOCHEMICAL PROPERTIES OF WATER-SOLUBLE CONTRAST MEDIA

Property	Significance
Solubility	Maximum possible concentration; where applicable, need to dissolve crystals in warmth before use.
Viscosity	Rate of injection; infusion. Highly viscous solutions can impair the microcirculation in selective angiography.
Osmolality	Pain in some angiographic indications; endothelial damage; arachnoiditis (?) in myelography; bradycardia in cardioangiography; hypervolemia after very rapid, high-dosed i.v. injection; diuresis
Lipophilicity, absence of hydrophilia (of ionic CM)	General reactions (nausea, vomiting, allergy-like reactions) more frequent, particularly at high dose and on rapid injection; protein binding, prevention of glomerular filtration; tubular secretion; biliary elimination; permeation through cell membranes, enteral absorption.
Electrical charge	Improvement of solubility; increases the hydrophilia; epileptogenicity

Table 4. The most important physicochemical properties of water-soluble, iodinated CM

The most important physicochemical properties of water-soluble, iodinated CM are their solubility, the viscosity and osmolality of the solutions, the lipophilic or hydrophilic properties of the iodine-containing molecule and the electrical charge (table 4). In practice, these properties have the following significance:

WATER SOLUBILITY

Very good water solubility is a prerequisite for the production of highly concentrated, radiopaque CM. As with sugars or peptides, the solubility of nonionic CM is mediated by hydrophilic groups (-OH, -CONH-). Some commercially available CM can crystallize at low temperature and must be dissolved again before use by warming up.

VISCOSITY/TEMPERATURE

The viscosity is a measure of the flow properties of the solutions and is expressed in millipascal · second (identical with the older unit centipoise). It strongly increases with increasing concentration and falling temperature (figs. 11, 12). The viscosity of the different CM is different at the same iodine concentration and same temperature (table 2).

This clearly affects the maximum injection speed, if e.g. narrow catheters or thin needles are used or if the injection of greater volumes is necessary. The injection speed can be given in mg iodine/second, as

this is the parameter which determines the contrast (table 5).

OSMOLALITY

Osmotic pressure

The osmotic pressure of a solution can be calculated in two different units, osmolarity and osmolality. The osmolarity is the concentration of osmotically active particles in relation to the volume of a solution. In the case of non-electrolytes it is identical to the molarity; for dissociated substances ≙ molarity times the number of ions in one mole; given as osmo/L solution. The osmolality describes the concentration of solute per kg of water.

The osmolality of CM solutions is expressed in milliosmol/kg water, in megapascal or in atmospheres (1,000 mosm/ kg = 2.58 MPa = 25.5 at). It is approximately proportional to the number of freely mobile particles (molecules, ions) per kg water. The osmolality of CM is dependent very much on the concentration and only slightly on the temperature (fig. 13). Different CM can display greatly diverging osmolalities at the same concentration of iodine (table 6). In the concentrations normally employed in angiography, all CM currently on the market are hypertonic in relation to blood.

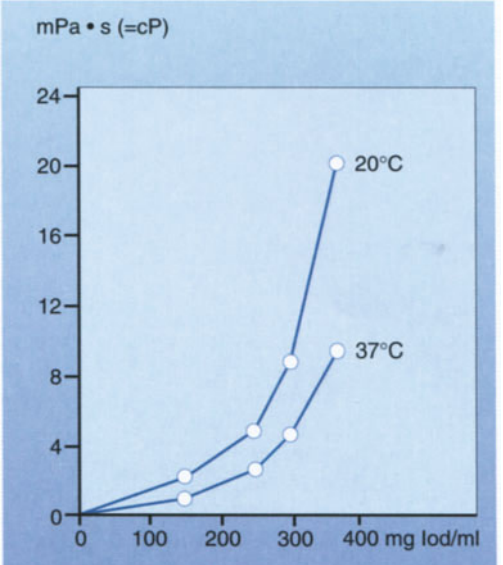


Fig. 11. Viscosity of Ultravist in relation to the concentration

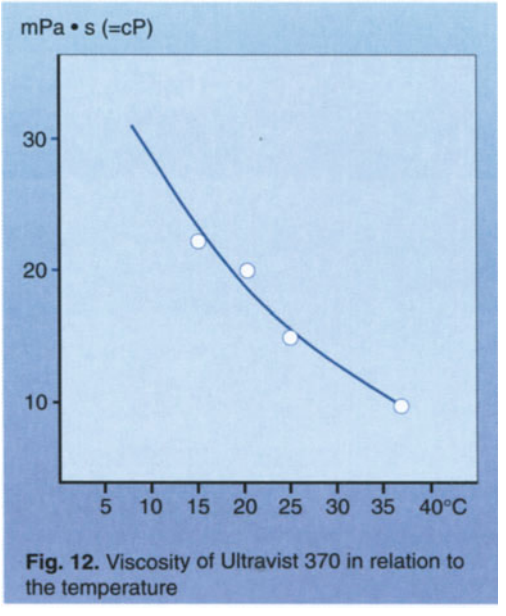


Fig. 12. Viscosity of Ultravist 370 in relation to the temperature

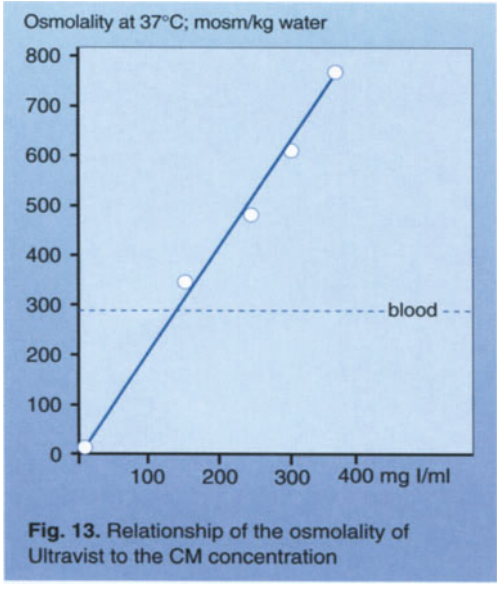


Fig. 13. Relationship of the osmolality of Ultravist to the CM concentration

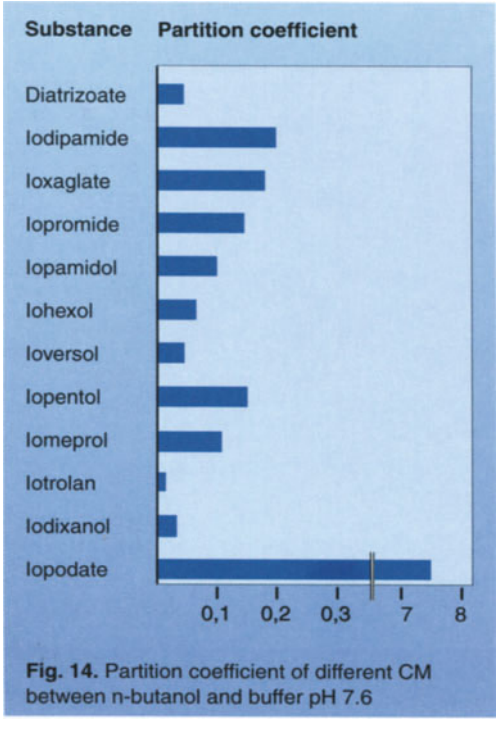


Fig. 14. Partition coefficient of different CM between n-butanol and buffer pH 7.6

HYDROPHILIA/LIPOPHILIA

The lipophilia of the iodine-containing CM acids or of nonionic CM is calculated from their distribution between a solvent (octanol, butanol) which is not miscible with water and an aqueous buffer with a pH value (distribution coefficient) close to that of blood or tissues (fig. 14).

The electrical charge (acid group) and the oxygen and nitrogen atoms in the side chains reduce the lipophilia of triiodobenzene, while methyl groups in the side chains increase it. CM for urography, angiography, CT and myelography should display as little lipophilia as possible. A correlation was found between lipophilia and certain types of side-effects when ionic contrast media are administered. This correlation was even more obvious if the degree of the binding of the contrast media to plasma proteins was measured rather than the lipophilia.

Non-ionic contrast media are generally very hydrophilic. The binding to plasma proteins is minor and does not correlate with the lipophilia, which is measured as a distribution coefficient (table 2 and fig. 14). It would seem that hydrogen bonds and other factors play a larger role as regards binding with proteins and the tolerance. Undoubtedly, the tolerance of these substances is also influenced by other factors which cannot be measured physicochemically.

Cholegraphic CM and particularly the oral ones must be very much more lipophilic (fig. 14).

ELECTRICAL CHARGE

Originally, the water-soluble CM were salts of iodinated organic acids. A contrast-producing iodinated anion in solution carries one or two negative charges, whereas non-contrast-producing cations (e.g. sodium, meglumine) each carry one positive electrical charge. Although the cations do not directly enhance radiographic imaging, they are essential for improving the solubility of iodinated acids and for attaining physiological pH values. Only acidic CM are effective as biliary contrast media, since only they are eliminated quickly enough by means of a hepatic anion transport mechanism. For all other indications, the new electrically neutral, nonionic CM have proven more suitable: the cations of CM salts unnecessarily increase the osmolality of the solutions and cause additional, generally undesired effects. The CM ions disturb the electrical potential on cell membranes. Electrical charge is the cause of a host of unwanted interactions of CM with the organism.

Others

Several other properties of X-ray contrast media are also of substantial signi-

	mg I/s
Ultravist-300	2027
Iopamidol-300	1974
Omnipaque-300	1753
Omnipaque-350	1477

Table 5. Maximum possible injection speed through an 5F Headhunter catheter, contrast media temperature 37°C, n = 20 per contrast medium [11]

		mg I/ml	Osmolality mosm/kg water
Blood			290
Ionic CM			
Urografin	30%	146	710
	45%	219	1050
	60%	292	1500
	76%	370	2100
Angiografin		306	1530
Urovist		306	1530
Hexabrix		320	577
Nonionic CM			
Ultravist		150	328 ± 4
		240	483 ± 17
		300	607 ± 9
		370	774 ± 10
Iopamiro		200	437 ± 16
(Japan, Australia, SA)		300	644 ± 31
		370	832 ± 34
Omnipaque		240	525 ± 15
		300	685 ± 10
		350	823 ± 23
Isovist		240	278
		300	291
Visipaque®		270	290
		320	290

Table 6. Osmolality of ionic and nonionic CM at 37°C; mean and 95% confidence interval

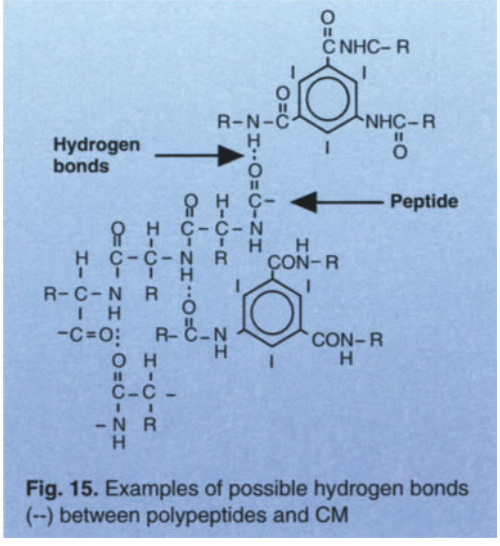


Fig. 15. Examples of possible hydrogen bonds (--) between polypeptides and CM

ficance. Binding to biomolecules can be mediated not only by the electrical charge and lipophilic groups but also by hydrogen bonds (fig. 15). Hydrogen bonds are responsible for the spatial arrangement of polypeptide chains (folding) and nucleic acids (helix). In many cases they determine the functionability of the macromolecule. The association of X-ray contrast medium molecules in concentrated solution must also be due primarily to hydrogen bonds.

Further relevant properties are, for example, the high density (the high specific gravity) of concentrated contrast medium solutions, which hinders the mixing of aqueous solutions with the blood, the (slight) buffering capacity, which effects the rapid assimilation of the pH value of the contrast medium to that of the blood and the powerful absorption of UV light, which is responsible for the light-sensitivity of the iodinated X-ray contrast media.

POSSIBLE USES OF X-RAY CONTRAST MEDIA

The possible field of applications of X-ray CM is wide. It ranges from the administration of CM with purely mechanical filling of certain cavity systems to opacification in a functional manner. In the latter case, the actual function of organs, such as the kidneys and liver, namely the elimination of metabolic end-products or exogenous substances, is exploited to demonstrate the organ itself or in the draining body cavities. As exogenous substances, the CM are eliminated from the organism via the kidneys and urine (urography) or via the liver and bile (cholegraphy) depending on their chemical structure and properties. As a consequence, parenchymal structures or elimination pathways become visible on the X-ray film (table 7a–c).

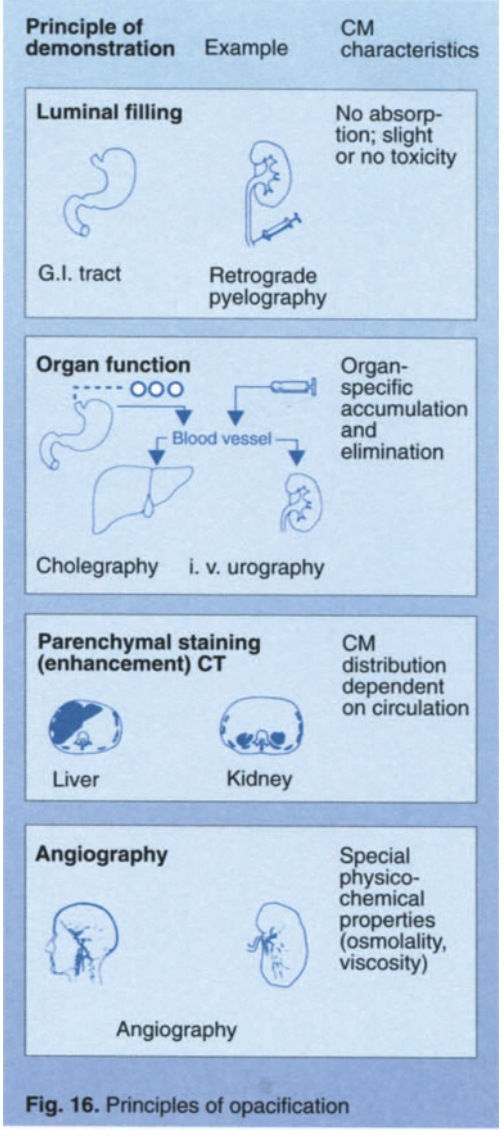


Fig. 16. Principles of opacification

PRINCIPLES OF OPACIFICATION (fig. 16)

The recognition of morphological structures is the main objective in direct luminal filling via a natural or iatrogenically (e.g. by puncture) created access; this permits the differentiation of superficial or mural changes. It can, however, also result in functional information, e.g. assessment of changes of tone or of the peristalsis in cavity systems (GI tract, ureters with retrograde filling, etc.).

In cavography, the concentration of the CM administered is decisive for the

degree of contrast in the radiograph. In urography and cholegraphy, on the other hand, the contrast density is essentially dependent on the functional capacity of the organs being examined. Consequently, assessment of both the functional capacity and the morphology is possible.

Thus, the radiological evaluation of the kidneys and the urinary tract or of the hepatobiliary system should contain not only morphological information, but also indications of functional changes of the respective organs. It can, therefore, provide important additional differential diagnostic information for the clinicians. As an example, the delayed elimination of renal CM can be interpreted as a definite indication of impaired glomerular filtration due to an acute or chronic process.

Another principle of use of CM has gained importance in CT. Initially, it seemed that the high absorption resolution of the method would make the use of CM unnecessary. In the meantime, the administration of CM has become routine in CT. The transit and accumulation of CM in the different organs (enhancement) improve the differentiation of morphological structures as a result of the differing enhancement, particularly between normal and pathological tissue. This allows or at least facilitates the demonstration of pathological processes and, occasionally, of their etiology as well.

Beyond this, evaluation of a section of the data from the complete scan obtained with the latest CT scanners allows the density pattern to be followed in the observed slice during the first few seconds after CM injection (dynamic CT). Conclusions can then be drawn about the functional status from the arrival and run-off and the pharmacokinetically induced distribution patterns of the CM.

Principle of demonstration	Method	Contrast medium	Dose (ml)	Iodine concentration (mg/ml)	Preparations	Peculiarities/ modifications
Luminal filling	**1.** G.I. study	$BaSO_4$	150 (–400)	–	(HD) Barium preparations	Hypotonia with scoplamine (20 mg i.v. or i.m.); faster passage with metoclopramide. In suspected perforation, suture insufficiency. Pediatric radiology; risk of aspiration and impaired pulmonary function
		+ CO_2	variable	–	CO_2 granulate	
		Renal CM	50–100	370 300 370 350 370	Gastrografin Isovist Ultravist Iohexol Iopamidol	
	G.I./CT		500–1000	10–20	30 ml/liter	
	2. Double-contrast of small bowel *(Sellink)*	$BaSO_4$ + methyl cellulose-containing water for DC	300 diluted with 600 ml H_2O	–	Barium preparations	Duodenal probe
	3. Colonic contrast	$BaSO_4$ + air	200 variable		Barium preparations	Hypotonia
	4. Arthrography	Urogr. CM + air	2–10 15–35	–	Isovist Ultravist Iohexol Iopamidol etc.	
	5. Sialography	Urogr. CM	1–3	300		
	6. Fistulography	Urogr. CM	variable	300		
	7. Hysterosalpingography	Urogr. CM	5–10	300		
	8. PTC, ERCP	Urogr. CM Urogr. CM	20–40 (10–40)	300		
	9. Retrograde pyelography (cystography)	Urogr. CM	5–10 (100–300)	300 150	Urovison R others	
	10. Myelography	Nonionic CM	15	240–300 200–290	Isovist Iohexol Iopamidol	
	11. Bronchography	Suspension		240–300	Propylidon Iopydol	

Table 7a. Overview of CM uses

Principle of demonstration	Method	Contrast medium	Dose (ml)	Iodine concentration (mg/ml)	Preparations	Peculiarities/ modifications
Organ function	**1.** I.v. urography	Urogr. CM	50–100	300–370	Ultravist Iohexol Iopamidol Iothalamate Ioxithalamate Urografin Urovison	Dehydration unnecessary with nonionic CM
	2. Infusion urography	Urogr. CM	100–250	150–300	Urovist	
	3. Oral cholegraphy	Oral cholegraphic agent	3–6 g		Biloptin and others	Admin. in 2 fractions
	4. I.v. cholegraphy	Biliary CM	20–30	180	Biliscopin Meglumine iodoxamate	Slow admin. essential
	5. Infusion cholegraphy	Biliary CM	50–250	30–80		
Parenchymal enhancement	**1.** Bolus-injection	Urogr. CM	1 ml/kg body weight or more	300–370	Ultravist Iohexol Iopamidol Angiografin	Administration immediately before examination. If necessary, scan series about 20 sec after injection
	2. Infusion		50–125	150–370	Meglumine Iothalamate Meglumine Ioxithalamate Urografin	

Table 7b. Overview of CM uses (cont.)

Spiral CT permits the 3-dimensional imaging of blood vessels following rapid injection of nonionic contrast media and the imaging of biliary ducts following administration of Biliscopin.

In angiography, selective opacification can be achieved by direct CM injection into a vessel. Diagnostic exploration then becomes possible not only of the shape and filling pattern of the vascular sections opacified, but also of the parts of the organ being

Principle of demonstration	Method	Contrast medium	Dose (ml)	Iodine concentration (mg/ml)	Preparations	Peculiarities/ modifications
Vasography	**1.** Cardioangiography	Urogr. CM	40–60	370	Ultravist Iopamidol Iohexol Urografin	
	2. Coronary angiography	Urogr. CM	5–8	370		
	3. Aortography	Urogr. CM	50	300–370	Ultravist Iopamidol Iohexol	Dose acc. to size of vascular region. Dose orientated on site of admin.
	4. Selective abdominal angiography	Urogr. CM	5-50	300		
	5. Peripheral angiography	Urogr. CM nonionic	10–70	300		
	6. Cerebral angiography	Urogr. CM nonionic	5–10	300		
	7. Phlebography	Urogr. CM	40	240–300	Ultravist Iopamidol Iohexol Meglumine salts <250 mg I/ml	
	8. I.v. DSA	Urogr. CM	20–50 ml per bolus	300-370	Ultravist Iohexol Iopamidol Urografin	
	9. I.a. DSA	Urogr. CM	As conv. angiography or less	75–300	As conv. angiography	The higher sensitivity of the method allows less selective injection, smaller volume or lower iodine concentration.
	10. Lymphography, direct	Oily CM	5–10/ extremity	480	Lipiodol (iodinated fatty acid derivative)	Intravascular administration

Table 7c. Overview of CM uses (cont.)

perfused. This, in turn, allows morphological and functional evaluation with great clarity of detail and a high yield of information.

Digital subtraction angiography (DSA) allows demonstration of the vessels without a disturbing background (e.g. bone) and with a very much lower CM concentration in the vascular regions of interest. The method is based on the subtraction of an image obtained immediately before CM injection from a series of images obtained under conditions of maximum CM concentration in the blood vessels involved.

In DSA, electronic amplification of only slight differences between the precontrast and the contrast images results in pictures of the vessels with very much greater contrast. In addition, electronic data processing speeds up the entire process considerably, so that the results are immediately available. Using this technique, larger arteries can be demonstrated even after an i.v. bolus injection of the CM. In i.v. DSA and fast CT high doses and rapid injection make particularly great demands on the tolerance of the CM; undisturbed cardiac function and pulmonary transit and the smallest possible sensation of heat or pain in the patient caused by the CM are prerequisites for a successful examination.

The CM suitable (type, concentration, amount) for the individual examinations are summarized in Table 7a–c.

PRACTICAL INFORMATION AT A GLANCE

Proper storage of contrast media	◆ in a dark place (e.g. in a cupboard) ◆ not near X-ray equipment for long periods of time ◆ at normal room temperatures (15–25°C) ◆ in a warming cabinet (37°C) not more than 3 months
Observation of expiry dates	◆ new products can be stored for a maximum of 2–3 years ◆ established products usually have a shelf-life of up to 5 years
Examination of the CM solution before use	◆ remove outer packing only shortly before use ◆ check clearness of solution (no discoloration, no cloudiness, no precipitates)
Cystallization found in solution	◆ can occur at low temperatures (in winter), heat CM solution briefly before use to 80°C
CM solution with high viscosity	◆ heat solution to 37°C, this reduces viscosity and allows solution to be drawn up better
Risks of microbial contamination	◆ do not keep opened vials and ampoules longer than one working day after first use; discard all remains at the end of the day
Resterilization of the CM solution	◆ do not resterilize opened containers
Transfer into sterile containers	◆ do not pour CM solution over the unsterile lip of the original container, keep it covered, and do not return it to the original vial

PURITY OF THE ACTIVE INGREDIENT, BY- AND DEGRADATION PRODUCTS

Because of the high doses employed – which can be more than 100 g substance per patient and examination – the demands made of CM in respect of their chemical purity are particularly high. The molecular structure of the CM substance is demonstrated by NMR, IR, MS and UV spectra (fig. 17a–d).

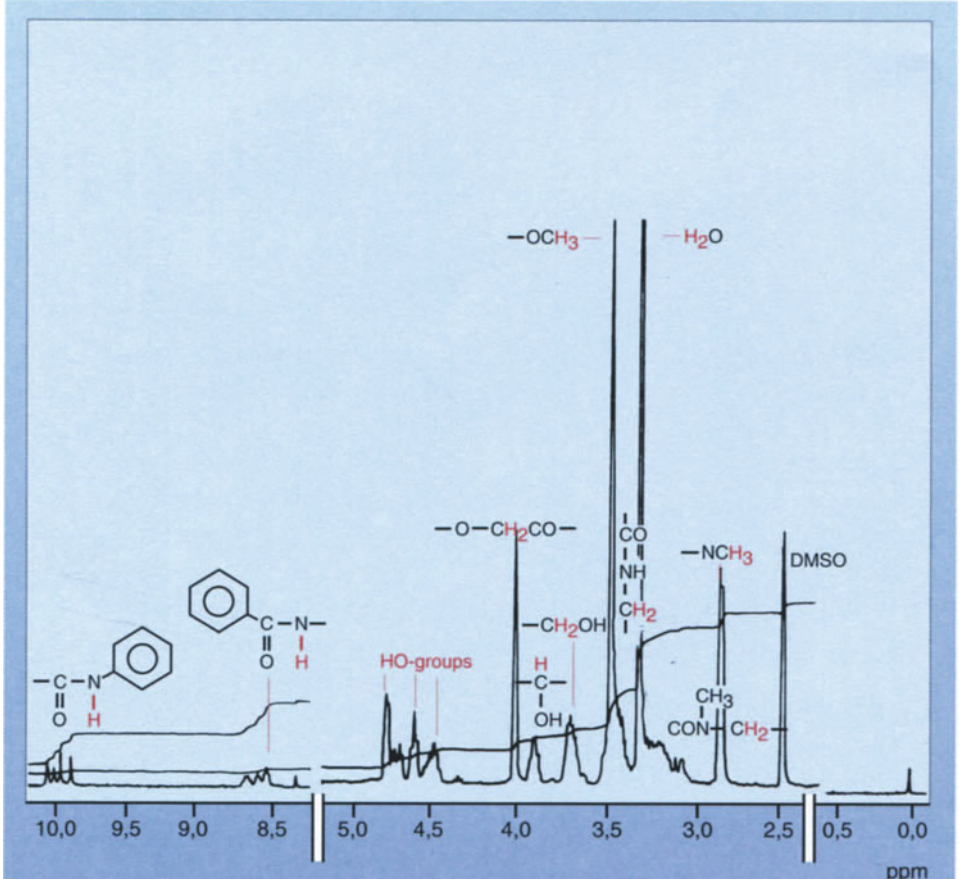


Fig. 17a. Proton-NMR spectrum of Iopromide in DMSO at 300 MHz

In addition, tests for foreign substances by means of thin layer chromatography (fig. 17e) and high pressure liquid chromatography are performed to detect any by-products originating from the synthesis [13, 14]. The total iodine content is calculated by means of micro-iodine determination following wet combustion of a sample; the active ingredient content is determined by spectral photometric measurement or HPLC. The prescribed values are 98–102%. In addition, tests for purity are performed using customary pharmacopoeia methods: among others, color, clarity and pH of a test solution; water content, sulfate ash, heavy metal contamination and tests for, among others, anorganic iodide and aromatic amine; TLC for foreign substances. Nonionic CM are also tested for ionic contamination by means of measuring their conductivity.

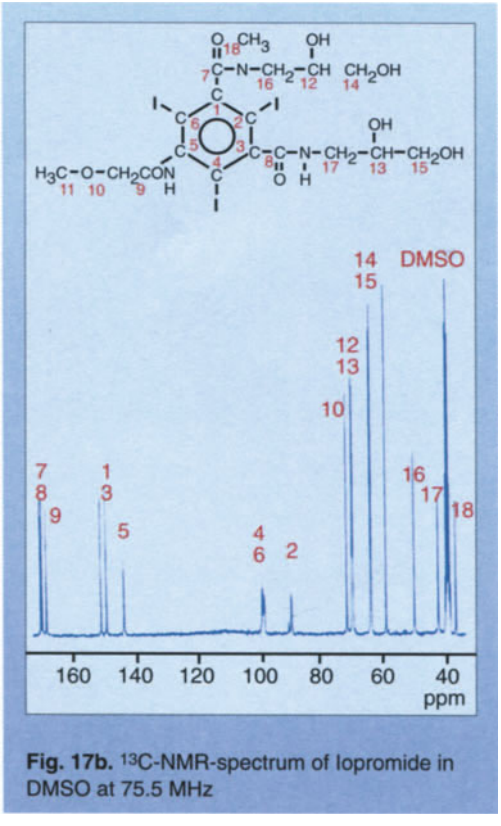


Fig. 17b. ^{13}C-NMR-spectrum of Iopromide in DMSO at 75.5 MHz

Two particular reactions are of importance as regard the storage of CM solutions: hydrolysis of amide bonds and the cleavage of inorganic iodide [15]. In the first case, either (additional) free carboxyl groups occur at the aromate (with a strongly acidic reaction) and aliphatic amines, or aliphatic carbonic acids and aromatic amines occur. The cleavage of iodine from the aromate leads to an increase of anorganic iodide in the solution; no elementary iodine is released. Degradation reactions of CM usually manifest themselves as changes in the pH value.

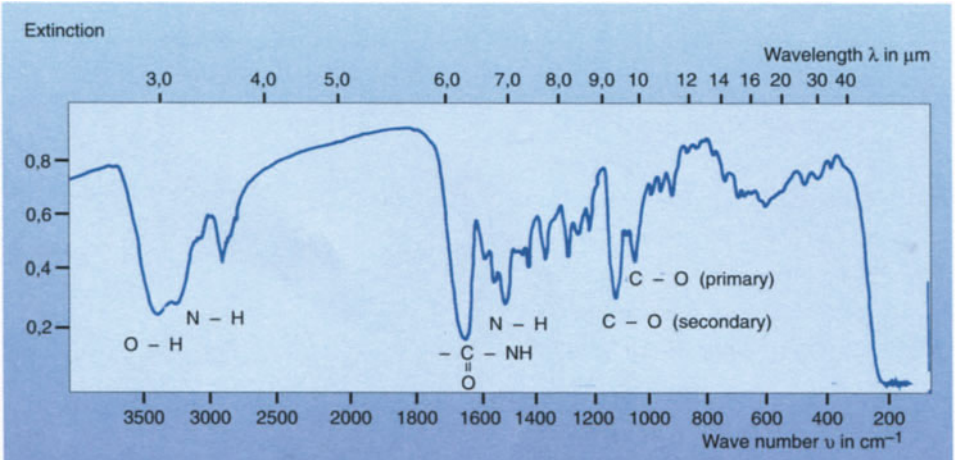


Fig. 17c. Infrared spectrum of Iopromide in KBr

FORMULATIONS

X-ray contrast media are usually offered as ready-to-inject aqueous solutions. Attention must be paid to the following properties as regards the use:

- type and amount of the active ingredient,
- where applicable, type or mixture of salts,
- iodine concentration in the solution in mg/ml.

The CM concentration is of less relevance to clinical use, since the other components of the CM – with the exception of the iodine – do not contribute to the opacification. There are, however, some exceptions:

Oral biliary CM are available in capsules or in another form suitable for ingestion.

ADDITIVES

In addition to the CM substance and the water, the finished preparations also contain pharmacologically relevant adjuvants.

$CaNa_2EDTA$ (calcium disodium ethylenediamine tetraacetic acid) is pharmacologically virtually inactive in the concentrations and dosages used. It is employed as a stabilizer in order to prevent the release of iodide from the organic bond caused by heavy metal catalysis, e.g. by traces of Cu^{++}. Na_4EDTA used to be employed for this purpose, but its calcium-binding property led to a reduction of cardiac contractility in cardioangiography. This effect is not observed with $CaNa_2EDTA$ [16]. The formulations of the nonionic CM Ultravist and Omnipaque each contain 0.1 mg/ml $CaNa_2$-EDTA.

Buffers can be added to CM in order to stabilize the pH value during storage. Tris and carbonate buffers, of which only low concentrations are required, are particularly suitable. The pH value of CM solutions lies approximately within the physiological range. The buffering effect is only slight. After injection, adaptation to the pH value of the blood quickly takes place. The formulations of Omnipaque and Ultravist contain 1.21 and 2.42 mg/ml Tris, respectively, with chloride as the counterion.

Preservatives (parabenes) may be present in CM for retrograde urography, while CM for oral ingestions for the demonstration of the G.I. tract may contain flavoring substances and emulsifiers.

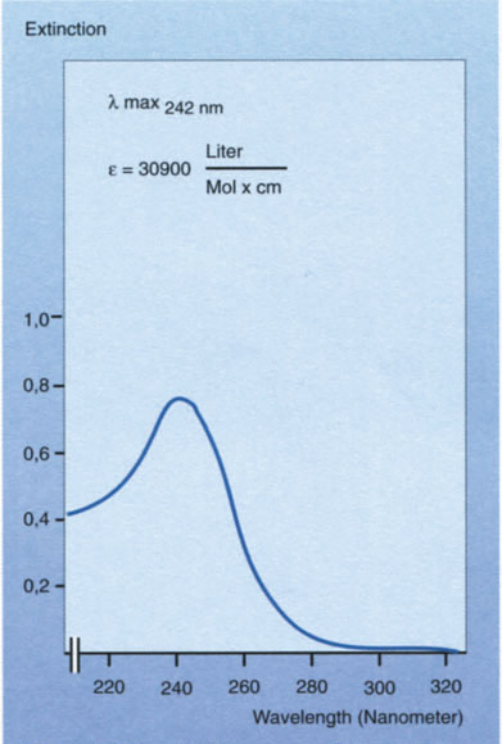


Fig. 17d. Ultraviolet-Spectrum of Iopromide in water (24 µg Iopromide/ml slice thickness = 1 cm)

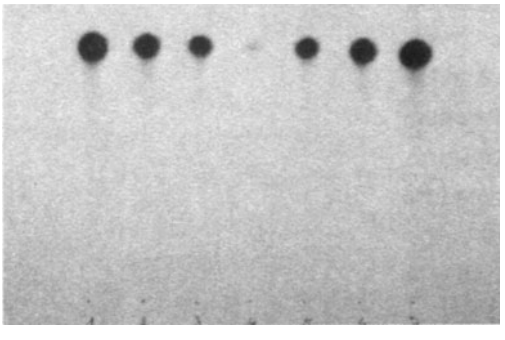


Fig. 17e. Thin layer chromatogram of iopromide on a silica gel plate 60F–254 (Merck). Solvent: Dioxane (85)-water (15)-ammonia (4). Amount applied form left to right: 200 µg, 100 µg, 50 µg, 1 µg, 50 µg, 100 µg, 200 µg. Photo at 254 nm

MICROBIOLOGICAL QUALITY OF THE FINISHED PRODUCT

Production under controlled environmental conditions

The manufacture of solutions for injection and infusion demands special hygienic measures which are determined by the construction of the production facilities, the technical installations and the competence of the workers.

Such manufacturers must meet not only the international and national guidelines of the health authorities, but also special requirements far in excess of these, e.g. those made on X-ray contrast media (fig. 18a-f).

Increasing microbiological purity is achieved by dividing the entire working area into three cleanliness classes:

CC I: Rooms which can be entered without changing, e.g. changing rooms, visitors' zone, air-conditioning plant.

CC II: Rooms which may be entered only after a change of shoes and outer clothing and with head covering. Preparatory work is done here.

CC III: Aseptic working zones. Change of CC II clothing to sterile clothing.

An air-conditioning system regulated centrally via microprocessors provides for the necessary environmental conditions at the individual workplaces. In the aseptic working zones, laminar-flow units – special filter units – additional to the conventional sterile air supply protect the product from the risk of contamination by man and environment.

Fig. 18a. Solution production and intermediate storage

Fig. 18d. Continuous sterilization

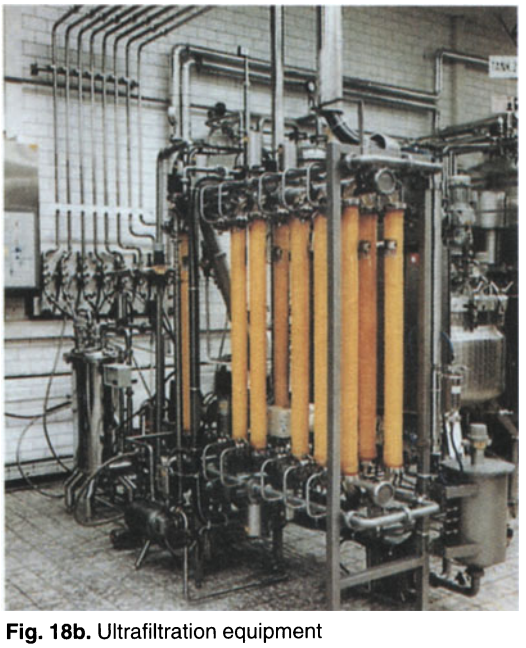


Fig. 18b. Ultrafiltration equipment

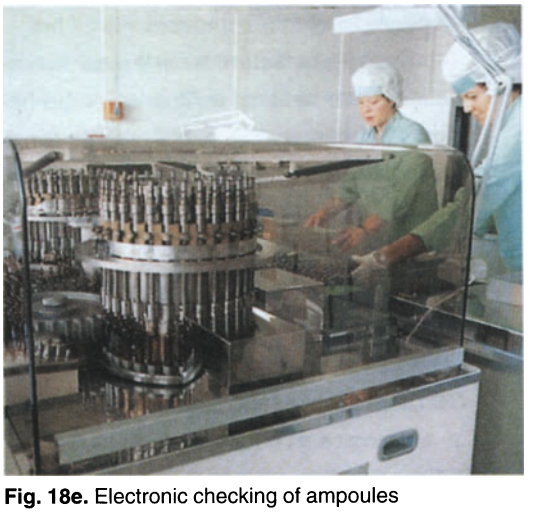


Fig. 18e. Electronic checking of ampoules

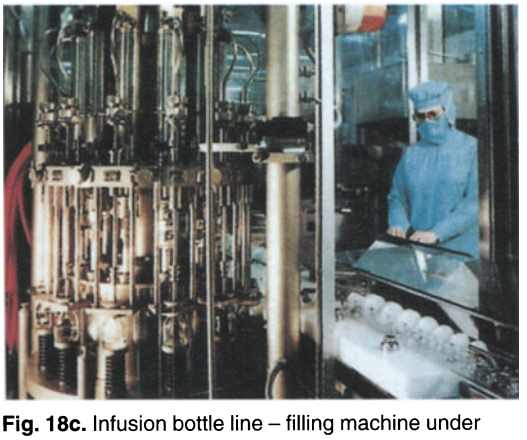


Fig. 18c. Infusion bottle line – filling machine under laminar flow

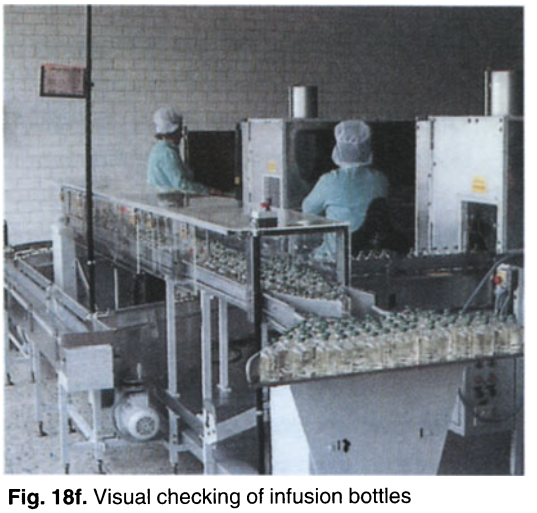


Fig. 18f. Visual checking of infusion bottles

The mechanical production lines have been automated as much as possible in order to reduce the risks which can arise through direct contact between man and product in this region as well. Examples are the computer-controlled cleaning processes for cleaning agitators, pressure tanks and other equipment.

The observance of all pharmaceutical rules and the proper use of the technical equipment require a qualified staff consisting of pharmacists, engineers, technicians and skilled workers which is able through routine training to make the best of the latest scientific and technical state of the art.

Production process

Table 8 shows schematically the production flow of CM manufacture in a simplified form.

Of interest here is the number of steps in the production. To ensure that every step takes place according to specifications, it is always followed by a process control. The result of such a process control shows that the concluded production step was carried out properly and that the next step can, therefore, start from a safe base. Thus, the sum of the individual process controls describes the quality of the finished product and says more about it than the finished article or final control, the result of which can only be based on a statistical pattern.

Let's just follow the production flow described in table 8:

The ingredients and packing material are checked as they come in and, after release by quality control, are brought on pallets to an intermediate store (CC II) after the outer surfaces have been cleaned.

The amounts of active substance and adjuvants specified in the prescription for a batch of the respective preparation are weighed in a weighing center and

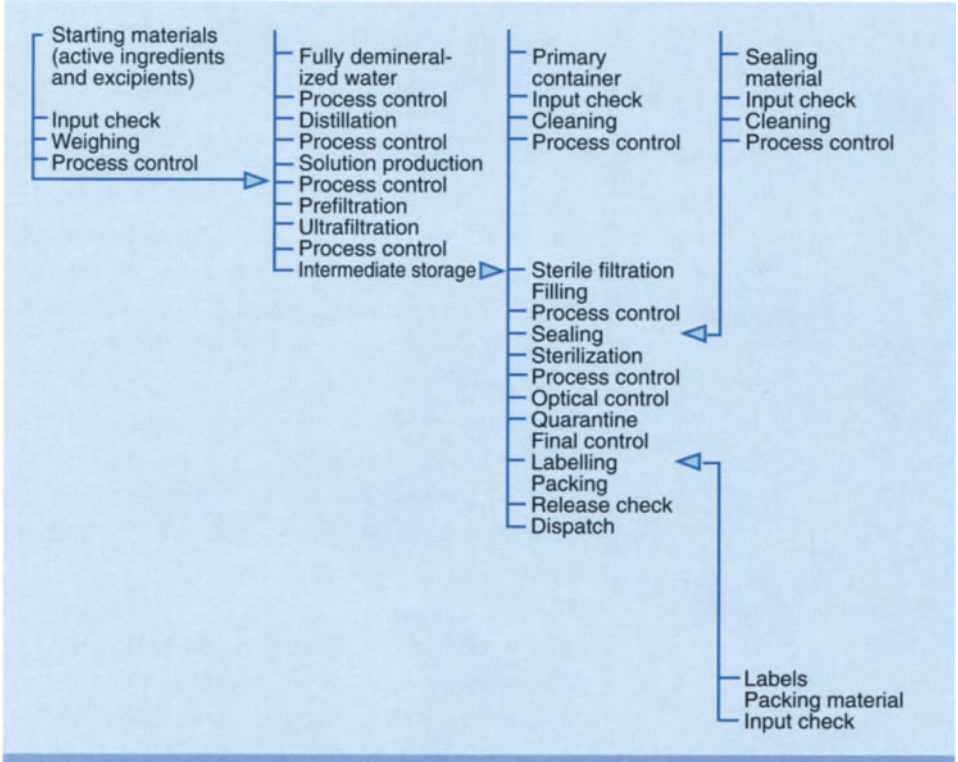


Table 8. Production flow scheme of contrast media

the data documented via an automatic control system. After an identity check, the substances are brought in special containers to the make-up rooms and dissolved in a stirring apparatus. The various chemical and physical data of the testing standard are checked before the solution undergoes sterile filtration. During filtration, all microorganisms and contaminating particles are sieved out of the solution. Particles down to a size of a 5,000th of a mm can be filtered out.

The solutions are now ready for filling and are led into the filling plant via a special system of pipes.

Ampoules are marked with the name of the preparation by means of a ceramic screen-printing proce-

dure. Vials and ampoules are cleaned, for instance by the additional use of ultrasound, sterilized, filled and sealed in a special cleaning, filling and sealing machine.

The process is accompanied by a check on the amount filled. Although the fact that the production rooms are aseptic means that filling can take place without contamination from the environment, the filling machines are further protected by a laminar-flow arrangement. The filled and sealed containers undergo final sterilization in steam autoclaves.

Finally, all filled articles are examined for possible mechanical contamination.

The finished batch of the drug is then moved to a quarantine store and, after a final check by Pharma Quality Control, released for packing.

Sterile filtration, ultrafiltration and sterilization

A constant check is kept on microbial contamination of all starting materials, such as the active ingredients, pure water, containers and stoppers.

Sterile filtration of the solutions and sterilization of the filled containers ensure the necessary sterility. In addition, what is known as molecular or ultrafiltration can be performed as, for example, in the case of the CM Ultravist. This process is able to retain molecules above a molecular weight of 10,000. It ensures that not only microorganisms, but also their high molecular weight metabolic products including pyrogens are withdrawn and the particle content in the lower micrometer range is distinctly reduced. In addition, the CM solution passes though a sterile filter while it is being filled into the ampoules or vials. Finally, the finished, firmly sealed individual containers are autoclaved for 20 min at 121° C. The containers are heated for the shortest possible time by superheated

steam and cooled again quickly by being sprayed with water. This is important because the chemical stability of the CM is limited in time at such high temperatures.

Sterility test

The object of the sterility test is to check whether microorganisms capable of multiplication can be demonstrated in the final product. The Millipore-Steritest system for two culture media is employed for the demonstration of sterility. The contents of 20 containers from each batch manufactured in the production line undergo membrane-filtration via the Steritest system: the membrane, which has an average pore diameter of ≤ 0.45 µm, retains any microorganisms present. The contents of each container are distributed evenly to two filter units and filtered. One filter is then coated with the culture medium casein-peptone/soya-peptone bouillon, the other filter with thioglycolate medium. The entire filter units are cultivated for 10 days. At the end of the cultivation period, the filter units are checked for macroscopically visible growth (turbidity). The sterility requirements are fulfilled when the culture media remain clear after brief shaking.

Test for pyrogens

Fever reactions can occur in man and animals after parenteral administration of injection and infusion solutions. The reactions are frequently caused by microbial metabolic and degradation products or endotoxins (constituents of the cell walls of gram-negative bacteria). These fever-provoking substances with a chemically heterogeneous structure are known as pyrogens.

The commonest internationally used test to demonstrate pyrogenic contamination in drugs is the in vivo pyrogen test in the rabbit. Rabbits react quickly

to the slightest pyrogenic impurity in an intravenously injected solution with an increase of body temperature. The method of testing is described in detail in the relevant pharmacopoeias. While the description of the actual testing procedure hardly differs in the pharmacopoeias of the individual countries, distinct differences exist as regards the evaluation of the results.

The LAL (limulus amebocyte lysate) test, an in vitro pyrogen test, is a limited alternative to the rabbit test. The limits to the use of the LAL test are set by the fact that it is only able to specifically demonstrate bacterial endotoxins.

PRESERVATION OF PRODUCT QUALITY IN HOSPITALS AND PRACTICES

After filling and sterilization, the CM undergo a final and thorough check for quality. Months or years may now pass before the products are actually used – a period in which the products are transported and stored under varying conditions. Finally, the vials or ampoules are opened or the stoppers are pierced; the CM solution is drawn up directly into syringes or automatic injectors. It may be infused through an infusion kit or be transferred to another container. The content of an ampoule or vial may be used up immediately after opening or, in the most unfavorable case, only after some time.

Transport, storage and all the manipulations which take place in the course of the actual use may impair the quality of a CM solution. A number of influences to which the products may be exposed after the final control by the manufacturer have been simulated in the laboratory and examined for their effect on the quality of the solutions. In every case, the user should

recheck the criterion clarity of the solution immediately before use (cf. also page 26, 37).

Stability in long-term storage and at different temperatures

One of the most important checks on CM solutions concerns the long-term stability. To ensure high quality up to actual use, every effort is made to develop the CM formulation and to choose the container materials in such a way that storage under normal conditions is possible for up to 5 years since insufficient experience is usually available at the time a new product is introduced to be able to prove such sustained stability; an expiry date (e.g. 2 or 3 years) is stated as a precaution.

The stability of CM is satisfactory at normal room temperature (15–25°C); there is no need to store the products in a cool place unless this is expressly mentioned on the label. Some compounds can crystallize at temperatures close to freezing point, e.g. during transport in winter. The crystals are usually easily recognizable and can be dissolved again in the unopened vial or ampoule by warming up briefly to max. 80° C. Contrast media generally tolerate such brief heating to this temperature without any problems, since they are heated to 121°C for 20 min after their manufacture for the purpose of final sterilization. The same naturally applies to warming the solution to body temperature before use to improve the tolerance. The subsequent sterilization of solutions from opened containers is, however, not permitted.

Although prolonged storage (for months or years) at higher temperatures (e.g. 30°C) does not usually lead to transgression of the limits set in the quality specifications, it should be avoided because of the accelerated degradation reactions compared to normal

pH value	6.5–8.0
Free amine	≤ 0.1%
Iodide	≤ 75 µg/ml solution
Color	≤ color of comparison solution B5 or BG5 or G5
Content of active ingredient	≤ 95–105%

Table 9. Features of quality and their threshold values with Ultravist 240 as the example

room temperature. It is not always possible to recognize CM which no longer meet the quality specifications from their appearance. Typical analytical changes are a decreased pH value and an increase of anorganic iodide and aromatic degradation products. Discoloration, turbidity and sedimentation can be recognized with the naked eye; these changes are an indication of imperfect quality. When stored correctly, i.e. protected from light and X-rays, and when observing the limits for storage temperature and duration, the critical values listed in table 9 will not be exceeded. Ultravist 240, Ultravist 300, and Ultravist 370 are still stable even after a storage period of several years at temperatures of both 20˚C and 30˚C (table 10).

Sensitivity to irradiation and light: white glass, brown glass, and UV-protective foil

X-ray contrast media are sensitive to light and, to some extent, also to irradiation. They should be stored in the dark and for only a limited time within the range of X-ray units. Although brown glass or UV-protective

	Storage period	Iodide (µg/ml)		pH value		Substance content as %	
		20˚C	30˚C	20˚C	30˚C	20˚C	30˚C
Ultravist 240	0	1		7.62		100	
50 ml	24 months	6	11	7.51	7.50	99	99
Ultravist 300	0	3		7.52		100	
50 ml	24 months	6	14	7.34	7.23	99	100
Ultravist 370	0	3		7.30		100	
50 ml	24 months	13	35	7.29	7.09	99	99

Table 10. Stability data for a nonionic CM

foil protects the solution to a certain extent from the influence of light, it has the big disadvantage that any particles which may occur (fragments of the stopper, crystals) are less easy to recognize. It is for this important reason that containers made of colorless glass are preferred. Because the glass is colorless, however, it is especially important that the outer packing (carton etc.) not be removed until shortly before use or that the CM be stored in a dark place, e.g. in a cupboard. During normal manipulation and use, exposure to light of normal room brightness (approx. 600 lux, cf. fig. 19) is not critical, but exposure to sunlight must be avoided.

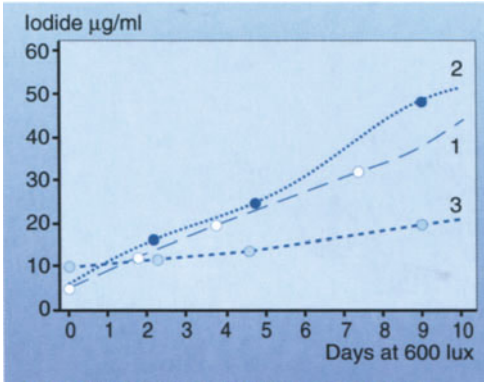


Fig. 19. Release of iodide from 3 different CM stored in a 50-ml clear glass vial and illuminated

The sensitivity to X-ray irradiation is quite low. Irradiation of up to 10 rd produced no relevant effect on either Urografin or Ultravist (table 11).

	Description Color	pH value	Iodide (µg/ml)	Free amine (%)
Urografin 30% nonirradiated	clear, colorless solution; < G6	6.63	3.7	0.006
Urografin 30% 1 rd irradiated	unchanged	6.62	3.6	0.004
Urografin 30% 10 rd irradiated	unchanged	6.62	3.6	0.006
Ultravist 300 nonirradiated	clear, colorless solution; G6	7.60	2.5	0.017
Ultravist 300 1 rd irradiated	unchanged	7.60	3.2	0.017
Ultravist 300 10 rd irradiated	unchanged	7.60	3.3	0.018

Table 11. Influence of X-ray irradiation on CM solution

Tests for contamination with particles

Particles in the X-ray CM solution must be avoided at all costs. They represent one of the most serious problems in the manufacture and handling because X-ray CM – unlike most infusion solutions – are injected not only intravenously, but sometimes intraarterially into the vessels of highly sensitive organs [17].

After their production, CM are checked very carefully for their content of the most minute particles. Particles subsequently occurring in closed containers may be CM crystals which appear in individual solutions when kept at temperatures close to or below the freezing point.

Vials showing flocculation must always be returned to the manufacturer. Crystals – when caused by storage at low temperature – can be dissolved again as described on page 26.

Other sources of contamination with particles can occur upon removal of the CM from the original container [18]. One possible cause is fragmentation of the stopper material. The punching-out of particles of rubber and the formation of rubber shavings cannot be avoided with all certainty when rubber stoppers are pierced by cannulas. This also applies, of course, to the sticker of infusion kits, although the kits offered by some manufacturers are fitted with appropriate fluid filters.

For testing purposes, the stoppers were fitted to normal vials and pierced with cannulas. After a total of 20 stoppers have each been pierced 5 times, i.e. after 100 piercings, the fragments are washed off, isolated on membrane filters and then counted. Comparative studies show that fragmentation is essentially dependent on the quality of cannula sharpening and on the caliber of the cannulas. The geometry of the stopper, especially the thickness of the membrane where

the stopper is pierced, and the stopper elastomer, its content of filler and the hardness likewise have an influence on the rate of fragmentation, but far less than that of the cannulas. Handling also has a considerable influence, of course. As an example, care must be taken on multiple removal of doses that the cannula is never inserted at exactly the same place twice. Since most of the CM are offered as so-called single dose preparations, however, this risk is avoided.

Even the shape in which the cannula is ground is important. Only cannulas ground to an acute or moderately acute angle should be used for piercing stoppers. Cannulas ground at an obtuse angle, e.g. those used as indwelling venous cannulas, increase the rate of fragmentation considerably. It goes without saying that the ground surface must be perfect. Cannulas which have become blunted, e.g. because they have been used several times and have hit against the bottom of the vial, are inappropriate.

The fragmentation rate obviously increases with the caliber of the cannula. Fragmentation of the stoppers increases decisively between 16G and 18G cannulas.

There is a temptation to use a larger cannula in order to shorten the time taken to draw up the solution, particularly when, for example, 50 ml of a relatively viscous CM solution are required. However, it is also possible to reduce the viscosity by about a half by warming the solution to 37°C. Moreover, so-called combi stoppers offer the possibility of eliminating the need to pierce the stopper and, instead, to remove it after tearing off the flanged cap. Of course, the solution can then only be drawn up with a syringe or with the syringe of a high-pressure injector. In the interest of sterility, the solution should not be poured out over the lip of the vial.

Finally, there is also a possibility of particle contamination from syringes and catheters, and this is likewise very difficult to detect.

Risks of microbial contamination

Triiodinated CM were originally developed from antibacterial substances. The ionic CM still on the market display distinct antimicrobial activity at least in the customary high concentrations (from 300 mg I/ml upward). This effect is attributable to two factors:

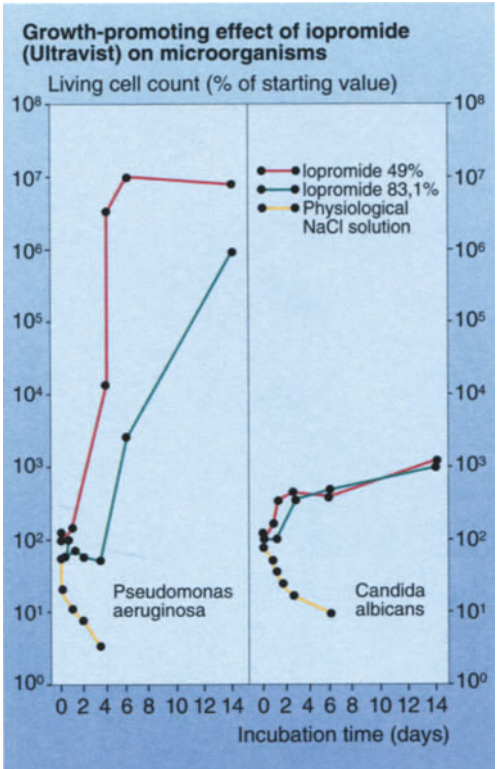

Growth-promoting effect of iopromide (Ultravist) on microorganisms
Living cell count (% of starting value)
Iopromide 49%
Iopromide 83,1%
Physiological NaCl solution
Pseudomonas aeruginosa
Candida albicans
0 2 4 6 8 10 12 14 0 2 4 6 8 10 12 14
Incubation time (days)

Fig. 20. Development of Candida albicans and Pseudomonas aeruginosa in aqueous solutions of a nonionic CM (Ultravist) at room temperature over a period of 14 days (incubation time)

- the high osmolality and
- a residue of chemotoxicity.

In contrast, nonionic CM are a good culture medium for fungi and bacteria because of their chemical composition and tolerance [28].

The behavior of microorganisms in a nonionic CM solution was studied in various Ultravist solutions (fig. 20). Six specimens of different groups of microorganism were used as representatives of a broad spectrum of pathogens. The risk of microbial multiplication and the spoiling of the product were simulated by artificial contamination in a model experiment:

- Three out of 6 types of microorganisms grew in Ultravist solutions:
  - *Pseudomonas aeruginosa* (gram-negative-bacterium, rod-shaped bacillus)
  - *Candida albicans* (fungus, yeast)
  - *Aspergillus niger* (fungus, mold).

- The growth of *Staphylococcus aureus* (gram-positive bacterium, coccus) was inhibited.
- The Ultravist solution displayed no effects on gram-positive, sporiferous bacteria: *Bacillus subtilis* (aerobic), *Clostridium sporogenes* (anaerobic). Neither an increase nor a decrease of the germ count was demonstrable here.

The risk of microbial contamination of the CM in the production zone can be kept low if, during the manufacture, filling and sterilization, the time between making up the solution and the subsequent antimicrobial treatment is kept as short as possible.

The following advice applies to the use of nonionic CM in particular:

- Careful avoidance of contamination of solutions and materials which come into contact with the solutions.
- Opened vials and ampoules to be used up in the course of one examination session if possible; keep for no longer than one working day after opening or removal of the first dose.
- All remains to be discarded at the end of a day to prevent their subsequent use.

Microbial contamination of CM solutions can, of course, only be recognized macroscopically at a very late stage. The typical finding in the case of fungal infections is a cloud of suspended particles resembling a cotton swab (fig. 21).

Fig. 21. Example of a microbially contaminated contrast medium solution. About 10 yeast cells were injected through the rubber stopper into the previously sterile contrast medium vial and then kept for about 3 weeks at room temperature. The development and maintenance of a fungal mycelium are pomoted by the viscosity of the solution

Transferring the contrast medium to sterile containers, disposable syringes, automatic injectors

Apart from the primary container (vial, ampoule), CM almost invariably come into contact with other ves-

sels, with syringes, tubes, catheters, injection needles etc.

Transferring to sterile vessels. Some X-ray examinations must be performed under absolutely aseptic conditions. In these cases, the CM is transferred to, for example, sterile vessels, since the unsterile outer surface of the original container would be a possible source of contamination. Measures to be followed here are:

- The CM solution should not be poured over the unsterile lip of the original container, but should be removed with a large-caliber cannula after complete removal of the stopper.
- The solution should be covered to prevent drying-out with the formation of crystals.
- The stability in an open container is, of course, limited to a short time; under no circumstances should solutions be returned to the original vial.

Drawing-up into disposable syringes or high-pressure injectors. When CM solutions are being drawn up from the original container into disposable syringes or filled into the syringes of high-pressure injectors, there exists – as with all opened vials – the risk of microbial contamination and subsequent multiplication as well as the possibility that ingredients of the plastic material or plunger will diffuse into the CM solution [19]. In all cases it is recommended that the CM is not drawn up into the syringes until immediately before use. Unused solution should be discarded after the end of the working day.

Table 12 shows a particularly unfavorable example. Constituents able to diffuse have been identified as 2-mercaptobenzothiazole and 2-hydroxyethylmer-

captobenzothiazole. They reach concentrations up to several µg/ml.

Use of large-volume CM bottles

For intravascular CM investigations large-volume, 500-ml, bottles are sometimes used for reasons of economy, easier handling and the better protection of the personnel against radiation. The contrast media are administered with automatic injectors or infusion pumps which are filled from the 500-ml bottles using appropriate transfer systems. Intentionally unfavorable conditions such as touching the surface of the stopper or the mini-spike with the fingers were created in carefully designed studies but only minimal contamination of the contrast media was found even then. No proliferation of micro-organisms in Ultravist® was observed within 24 hours [61, 62]. Likewise, under the conditions of angiography no relevant microbial contamination had appeared by the end of the angiographic examination when Ultravist® was left in open vessels [63].

Hours	$E_{280\ nm}$	pH
0	0	6.8
1	0.05	6.7
2	0.10	6.3
4	0.16	6.6
7.5	0.29	6.2
22	0.57	6.3
24	0.58	6.4

Table 12. Alteration of an unbuffered aqueous solution in a disposable syringe caused by substances entering the solution from the syringe material and which absorb at 280 nm

Resterilization. The wish sometimes occurs to produce a stock of dilute, nonproprietary CM solutions or to transfer CM to containers not supplied by the manufacturer and to store them for prolonged periods of time. Resterilization of the solutions then becomes a consideration. It must be said in this connection that a freshly produced solution of a chemically sufficiently stable CM such as Ultravist is quite able to withstand a second heat sterilization (20 min, 121°C) without any serious signs of degradation. Resterilization cannot, however, be recommended under the conditions prevailing in practice (opening of the original container, unknown interaction with the new container, the effect of preceding, regular storage on the CM). Sterile-fil-

tered solutions should likewise be used within 24 hours of production, or else discarded. The newer CM make such good culture media that sterile filtration cannot be considered adequate as a method of sterilization.

INFLUENCE ON LABORATORY TESTS

The influence of different ionic and nonionic CM on the results of the determination of clinicochemical parameters in serum and urine was examined systematically in the laboratory of Dr. Junge, Germany. For this purpose, reference sera (normal and pathological values) were mixed with up to 20 vol.% CM solution and urine with up to 50% CM solution. Higher concentrations than this are unlikely to occur even a very short time after a CM injection.

It was found that measurement of the serum enzymes GOT GPT, γ-GT, AP, LDH, HBDH, CK, CKMB, ChE, GDH, amylase (with maltotetraose, Biomed) and lipase (Automatic Clinical Analyzer, Du Pont) is not disturbed by Ultravist, Urografin (diatrizoate) or iohexol. Meglumine-sodium ioxaglate caused suppression of GPT.

Similarly, the urinary enzymes γ-GT, LDH, AAP, β-NAG and amylase were not or only slightly influenced by the CM mentioned. The specific gravity of urine increases after administration of iodinated renal CM.

The determination of protein by means of the biuret method was not disturbed by Ultravist, but was sometimes greatly disturbed by other CM; on the other hand, the measurement of protein in urine using the ponceau-S method was not affected.

The determination of the substrates BUN, creatinine, uric acid, bilirubin (direct and indirect), glucose, cholesterol and triglycerides was not recognizably affected by Ultravist. In contrast, other CM caused deviations – some marked – in individual parameters.

Measurement of the electrolytes (particularly iron and copper) was affected by all the CM tested and very much so by some.

In case of doubt, the samples for serum or urinary analysis should be obtained either before CM administration or at the earliest 24 hours afterwards. In patients with severe renal failure, it may be necessary to wait even longer because of the delayed elimination.

All tests concerning the thyroid gland can be disturbed for far longer than 24 hours by the iodide administered with the CM. The ability of the thyroid tissue to take up radioisotopes for the diagnosis of thyroid disease is reduced by iodinated renal CM for 2–6 weeks.

Urographic CM affect laboratory test results least, and orally administered cholegraphic agents and iodinated oily CM have a longer-lasting effect.

INTERACTION WITH MEDICINES

To date, some interactions of CM for urography, angiography and CT with medicines have been described in association with clinical use. Since these CM bind hardly at all to plasma proteins, cause no inhibition of enzymes, are not themselves subject to metabolism and are not absorbed enterally, such interactions are also extremely improbable.

In tumor patients who have been treated with **interleukin-2**, a higher frequency of side-effects has been observed after administration of ionic and non-ionic contrast media. These side-effects manifested themselves as fever, nausea, vomiting, skin reactions, diarrhea etc. [35, 36]. On the other hand, **buscopan** appears to have no influence on contrast media tolerance [12].

Due to the risk of lactate acidosis it was originally recommended that the treatment with biguanides (Glucophage®, Metformin) should be withdrawn two days before the application of intravascular x-ray con-

trast media in order to avoid the accumulation of the exclusively renally excreted Metformin should contrast medium-induced renal failure occur. This objective would, however, also be achieved if the biguanide therapy were to be withdrawn from after the administration of the contrast medium until it has been ascertained that the kidney function has not been impaired by the examination with a contrast medium [64].

A variety of pharmaceutical substances have been tested in animal-experimental studies for their influence on the acute tolerance of CM. Even here, interactions were seldom found which could be presumed to be of any clinical relevance [20, 21].

In cardioangiography, there is a possibility that the cardiodepressive effect of ionic CM caused by calcium binding will be intensified by **calcium blockers** (verapamil) [22].

The literature contains a reference to the possibility of complications if Isovue 370 is used concomitantly with **papaverine** in angiography. In one case thrombotic occlusion of the arterial circulation in the lower extremities which could not be alleviated with continuous urokinase infusion was observed [65].

Patients with cardiac insufficiency and renal dysfunction undergoing angiography should not be given **furosemide** (diuretic) – even with large quantities of liquid. Patients who received 110 mg furosemide additional to 3 liters of fluid exhibited a creatinine rise from 145 ± 13 to 182 ± 16 µmol/L, whereas the controls without furosemide showed no rise [66].

There are also indications that **neuroleptic agents** (chlorpromazine) potentiate the normally only slight epileptogenic effect even of nonionic CM in myelography [23].

Cholegraphic agents bind to plasma proteins and are eliminated with the bile via an active transport

mechanism which is limited in its capacity. They are able to displace drugs and endogenous substances, as long as they have the same properties. In this way, the concentrations of free drug in plasma can be increased by the simultaneous administration of biliary CM and their excretion delayed to some extent.

The absorption of oral cholegraphic agents presupposes their passage from the stomach into the bowel. Drugs which affect the gastric passage, therefore, simultaneously alter the rate of absorption of CM. The same effect is likely in the case of substances or foodstuffs which have an influence on the absorption of pharmaceutical substances from the bowel (e.g. carbon, gel-forming substances, fats, coffee etc.).

INTERACTION OF CONTRAST MEDIA WITH ADDITIVES AND DURING INTERVENTIONAL PROCEDURES

In the course of some diagnostic or interventional radiological measures, the X-ray contrast media are treated in a special manner, mixed with therapeutics or come into contact with locally high concentrations of equally undiluted drugs in the body. In such cases, it is possible that precipitations of the contrast medium, the therapeutic, both together, the inactivation of drugs or other undesirable and sometimes hardly predictable effects could occur (Table 13).

EFFECTS ON BLOOD COAGULATION

Nonionic contrast media resemble the ideal of completely pharmacologically inert substances much more closely than ionic contrast media. Ionic contrast

	Ionic CM	Nonionic CM
Heating of the contast medium up to 100°C e.g. for embolization	possible	possible
Mixing with ethanol	?	possible
Mixing before injection		
Papaverine[a)]	precipitation	remains clear
Tolazoline[b)]	precipitation	remains clear
Diphenhydramine[a)]	precipitation	remains clear
Prostaglandin E1[c)]	remains clear	remains clear
Pheniramine[c)]	remains clear	remains clear
Cimetidine[a)]	precipitation	remains clear
Na-Heparin[a)]	remains clear	remains clear
Protamine[a)]	precipitation	remains clear
Vasopressin[c)]	remains clear	remains clear
Adrenaline[a)]	remains clear	remains clear
Hydrocortisone Na-succinate[a)]	remains clear	remains clear
Methylprednisolone Na-succinate[a)]	remains clear	remains clear
Lidocaine[b)]	remains clear	remains clear
Diazepam	precipitation	remains clear
Nitroglycerin[b)]	remains clear	remains clear
Ampicillin[a)]	remains clear	remains clear
Erythromycin[a)]	remains clear	remains clear
Gentamicin[a)]	remains clear	remains clear
Chloramphenicol[c)]	remains clear	remains clear
Urokinase	remains clear	remains clear

* 50% loss of efficacy with Ultravist added corresponding to 170 mg I/ml or Isovist 300 mg I/ml
a) [37] b) [38] c) [67]

Table 13. Data on interactions found in the literature

media inhibit the enzymes involved with blood coagulation as well as other processes more strongly than nonionic X-ray contrast media.

Ionic X-ray contrast media are

- more toxic
- more anticoagulative

Sample	Coagulation time in sec.
Plasma without additives	11 (10.5–10.9)
Plasma + physiol. NaCl	12 (11.9–12.0)
+ Angiografin	68 (68.0–69.5)
+ Ultravist-300	17 (16.4–16.8)

Table 14. Determination of the thromboplastin time of human plasma without and with the addition of 25 volume percent test solution; n = 4, mean and 95% confidence limits

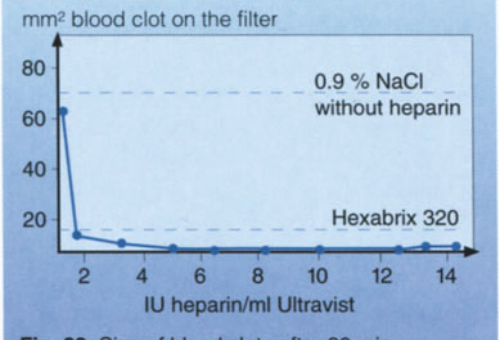


Fig. 22. Size of blood clots after 90 min. Incubation of 2 ml human blood in 10 ml plastic syringes with 5 ml test solution; not mixed, maximum contact surface

Nonionic X-ray contrast media are

- better tolerated
- less anticoagulative

The anticoagulative effect of contrast media is viewed by some radiologists as additional protection against the occurrence of thrombi during imperfect performance of catheter angiography. Contrast medium residues in the catheter lumen or even in syringes should prevent the receding blood from coagulating.

Laboratory examinations have shown significant differences in the anticoagulative effect of ionic (e.g. Angiografin) and nonionic contrast media (Ultravist) (table 14).

By adding small quantities of heparin to nonionic X-ray contrast media, an effective inhibition of blood coagulation can be achieved which is similar to that which is characteristic of ionic contrast media (fig. 22). It was shown that 5 IU heparin/ml Ultravist is sufficient to completely suppress the formation of thrombi under standard experimental conditions. Even with a volume of 300 ml heparinized contrast medium, no systemic anticoagulative effects should be expected. The good tolerance of the nonionic contrast medium remains unchanged.

Handling is similar to the preparation of heparinized physiological NaCl solution, which is used to rinse the catheter during an examination: the heparin is added to the contrast medium immediately before administration. The minimal dilution of the contrast medium has no effect on the contrast. Thorough mix-

Solution	Immediately after addition	2 h pre-incubation heparin/CM	4 h pre-incubation heparin/CM
Physiological NaCl	7		
Ultravist	11		
Ultravist-300			
+ Heparin "Novo"	30	29	23
+ Heparin "Medac"	30	30	28
+ Thrombophob "Nordmark"	36	32	33
+ Heparin-Na "Braun"	44	38	34
+ Liquemin "HLR"	38	23	32
+ Heparin-Ca "Radiopharm"	37	no coagulation	no coagulation
+ Heparin-Ca "Braun"	21	99	108

Table 15. Thromboplastin time of human plasma with the addition of 25 volume percent test solution (n = 3, mean values); heparin concentration 5.66 I.U./ml solution

ing is necessary because of the difference in densities.

The stability and anticoagulative effect of the contrast medium was tested 4 hours after preparation. No change was seen with Na-heparin; Ca-heparins showed an increase in effect with time (table 15).

RISKS OF CONTRAST MEDIA USE

The object of CM is to help to visualize certain structures in the organism or also to provide information about organ functions. An important prerequisite for a CM is low toxicity and safe use, since CM are often injected in high dosages and, for certain purposes, very quickly.

IONIC CONTRAST MEDIA

Extensive statistics are available on the side effects of ionic CM. The incidence of reactions depends on a large number of factors, such as the patient's condition, the kind of examination (table 16), the type of CM, its dose and also the conditions under which the examination is being conducted. Special attention has, of course, been devoted to the frequency of severe and fatal CM incidents. The available statistics (table 17) diverge greatly. Common to all of them, however, is the finding that, with the ionic preparations, even fatal CM incidents are not very rare events compared with the frequency of use of these substances.

Kind of examination	No. of patients	Incidence of side effects (%)	No. of deaths
Urography	214033	10257 (4.80)	11
Cholangiography	33778	2676 (8.00)	2
Cerebral angiography	12771	263 (2.06)	1
Angiocardiography	7911	179 (2.26)	2
Aortography	24885	665 (2.67)	1
Other angiographies	2815	101 (3.58)	0
Venography	5890	160 (2.72)	1
Total	302083	14301 (4.73)	18 (0.006%)

Table 16. Incidence of side effects in various CM examinations (32), ionic CM exclusively

NONIONIC CONTRAST MEDIA

1 : 116000 Pendergrass, USA	1960
1 : 85000 Toniolo, Italy	1966
1 : 61000 Wolfromm, France	1966
1 : 40000 Ansell, U.K.	1970
1 : 53000 Fischer, USA	1972
1 : 30000 Witten, USA	1973
1 : 10000 Shehadi, USA	1975
1 : 20000 Shehadi, USA	1980
1 : 75000 Hartmann, USA	1982

Table 17. Risk of death with i.v. urography

Nonionic contrast media are much better-tolerated than ionic contrast media in many ways (table 18). A number of trials have investigated especially the frequency of general reactions after intravenous administration of nonionic X-ray contrast media (table 19). Some of these investigations have been performed in comparison to conventional ionic X-ray contrast media. A sufficient number of cases were examined to make statements regarding the frequency of severe reactions. At this point, it is not possible to make statements about the frequency

▼ poorly tolerated ▲ much better tolerated ● no significant difference or difference not proven

	Conventional ionic RCM	Low osmolar ionic RCM	Non-ionic RCM
General reactions (nausea, vomiting, allergoid side-effects, some cardiovascular reactions)	▼	▼	▲
Neural tolerance	▼	▼	▲
Osmolality-dependent effects (pain, vasodilation, bradycardia, diuresis etc.)	▼	▲	▲
Calcium binding (cardiodepression)	▼	▼	▲
General renal tolerance, i.v.	●	●	●
Renal arteriography	▼	●	▲

Table 18. Differences in tolerance between the individual types of X-ray contrast media for urography, angiography and CT

Trial	Nonionic CM Side-effects total	Nonionic CM Side-effects severe/ very severe	Ionic CM Side-effects total	Ionic CM Side-effects severe/ very severe
Schrott [39] 50,660 cases	2.1%	0.01%		
Palmer [40] 30,268 nonionic cases 79,278 ionic cases	1.2%	0.02%	3.8%	0.09%
Katayama [33] 168,363 nonionic cases 169,284 ionic cases	3.1%	0.004%	12.7%	0.04%

Table 19. Frequency of side-effects during intravenous injection of nonionic and ionic x-ray contrast media (severe/very severe reaction requires that the patient be immediately hospitalized)

of deaths related to the use of nonionic contrast media. However, it is very likely that nonionic X-ray contrast media are less frequently related to fatalities as life-threatening conditions (unconsciousness of the patient, conditions requiring an anesthetist etc.) occur much less often.

On the other hand, it must be observed that all of the known types of side-effects associated with ionic contrast media can also occur during the administration of nonionic contrast media. Only the frequency has actually changed. One must, therefore, always be prepared to treat contrast media reactions.

DELAYED REACTIONS

Following the introduction of nonionic contrast media, reactions have been reported which are first noticed hours or even days after contrast media administration. A comparative study (Conray as the ionic contrast medium and Iopamidol as the nonionic contrast medium) showed a somewhat greater frequency for the symptoms erythema and possibly parotitis after

administration of Iopamidol. The total number of delayed reactions was the same for both contrast media, however [39].

Another comparative study (Iohexol and Iopamidol) performed by computer tomography involved 2382 patients. Reactions delayed by up to 2 days were twice as common as reactions occurring in the first 30 minutes. Headache and rash were the most frequent delayed reactions. Although all delayed reactions were mild in their intensity the attending physician should draw the patient's attention to the possibility of delayed reactions [69].

A greater frequency of allergy-like delayed reactions has been observed in intravascular administration of nonionic dimeric X-ray contrast media. These also included severe events lasting for several days and requiring therapy. They were, however, rare. The causes, risk factors, mechanisms of action and the actual frequency especially of severe delayed hypersensitivity reactions remain unknown despite concerted efforts to clarify them. The current state of knowledge has been the subject of special symposia.

The German health authorities have initiated a graduated plan for the intravascular administration of dimeric nonionic contrast media and have introduced restrictions on their use.

CAUSES OF CONTRAST MEDIA REACTIONS

Contrast media side-effects generally cannot be explained by a single mechanism [24]. The type of contrast-giving substance and its particular pharmacological properties, the examination technique employed, such as the size of the dose and the mode of administration, and finally, the patient's apprehension, are all

regarded as important contributory factors. CM side effects can be classified in several ways, but the most appropriate is by their cause.

Classification by cause:

- General or largely dose-independent CM reactions (anaphylaxis).
- Chemotoxic, local and cardiovascular effects, side effects dependent on the dose.

GENERAL REACTIONS (ANAPHYLACTOID REACTIONS)

General or CM reactions can range from mild reactions, such as urticaria, via moderately severe reactions, such as bronchospasm, and severe reactions, such as collapse or even cardiac arrest, to a fatal outcome. Severe and fatal reactions are rare. The mortality reported for conventional ionic CM is one in every 10,000 to 100,000 patients.

In 1997 the adverse events in response to the administration of X-ray contrast media spontaneously reported to the US Food and Drug Administration between 1978 and 1994 were published [71]. The

Intensity of adverse events	Ionic RCM Frequency of adverse events (%)	Nonionic RCM Frequency of adverse events (%)
Mild/moderate	18,400 (88.4%)	3586 (81.2%)
Severe	1737 (8.3%)	626 (14.2%)
Fatalities	685 (3.3%)	204 (4.6%)
Total	20.822 (100%)	4416 (100%)

Table 20. Adverse events following intravascular injection of X-ray contrast media spontaneously reported to the Food and Drug Administration (USA) between 1978 and 1994 [71]

frequency of reported adverse events cannot be unquestioningly related to the frequency of use of contrast media. It is noticeable, however, that the ratio of mild and moderate to severe adverse events and to the number of fatalities reported under ionic and nonionic agents is almost the same (table 20) and that the annual number of severe, not fatal events reported in the years 1992–94 under the nonionic agents was not higher than under the ionic agents (fig. 23), although the nonionic preparations were used more often and were preferred in high-risk patients and higher-risk examinations.

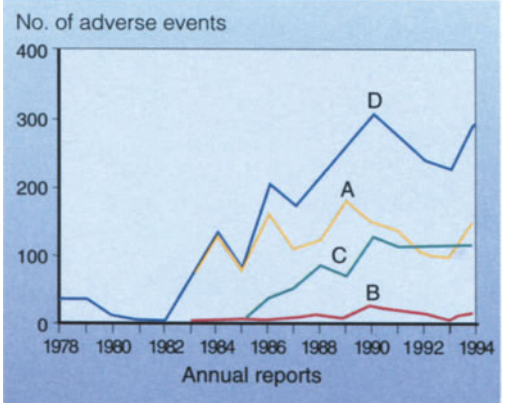


Fig. 23. Spontaneous annual reports to the FDA (USA) of severe non-fatal x-ray contrast media adverse events (1979–1994), A = high osmolar RCM, B = low osmolar ionic RCM, C = nonionic RCM, D = total [71]

These reactions may occur in any patient without any warning whatsoever. Because of this, the examining doctor must be prepared for all emergency measures, such as medicinal therapy and artificial respiration.

General or CM reactions have little or nothing to do with the osmolality of the CM. They can occur after administration of very small amounts of diluted and even isotonic CM. They are observed most frequently after i.v. administration, but also in arteriography and other examination procedures.

The following have been suggested as the mechanisms for general or CM reactions:

- An effect on plasma protein, the complement system, blood coagulation and/or the vascular endothelia,
- an effect via the central nervous system and
- a cross-reaction of the CM with antibodies which were not, however, originally formed against the CM.

PROPHYLAXIS OF GENERAL REACTIONS

In the meantime, it is regarded as confirmed that nonionic CM cause such reactions considerably less frequently than ionic CM and, in particular, less frequently than the low-osmolar, ionic compound meglumine-sodium ioxaglate [33, 34].

In many cases, nonionic CM are tolerated without symptoms even by patients who have exhibited repeated and predictable reactions to the injection of ionic CM [4, 29].

In recent years, a prophylactic effect in respect to general CM reactions after administration of conventional ionic as well as nonionic preparations has been demonstrated for certain therapeutic regimes, e.g. the oral administration of 32 mg methylprednisolone* 6–12 and 2 hours before the examination or the combined administration of H_1** and H_2*** blockers [30, 31]. The prophylaxis consists in a reduction of the frequency of anaphylactoid reactions, but in no way are such reactions definitely ruled out by the suggested measures. It can also not be expected that the frequency or severity of any reactions other than anaphylactoid side effects (e.g. neural, renal, most cardiovascular reactions or pain) will be reduced by prophylactic treatment of the patient with corticoids or histamine receptor blockers.

With patients at risk (allergic and cardio-pulmonary patients), the prophylaxis with H_1 and H_2 blockers leads to a significant reduction in the frequency of side-effects, even using nonionic X-ray contrast media; patients without risk factors received no benefits from the prophylaxis [40].

What is certain is that calm and assured management of the patients and distraction of their attention during the examination can help to avoid side effects.

* 2 tablets methylprednisolone 16 mg

** H_1 blocker: Dimetindene maleate; intravenous injection of 0.2 mg/kg b.w.

*** H_2 blocker: Cimetidine; intravenous injections of 5 mg/kg b.w.

DOSE-DEPENDENT SIDE EFFECTS

The distinctly dose-dependent side effects are, for example, a sensation of pain and heat, circulatory disturbances and renal damage. These side effects are attributable to the osmolality and pharmacological effects, and it is not always possible to differentiate between these two components.

Nonionic CM all have a distinctly lower osmolality than conventional ionic contrast agents and have among others therefore replaced ionic contrast media to a significant degree.

The advantages of nonionic CM are especially obvious in:

- Pain-intensive applications, since the osmolality is the main factor as regards the painfulness of a contrast medium.
- Angiographic examinations with high dosages caused by a number of single injections, e.g. cardioangiography, femoral arteriography, the demonstration of several vascular regions with conventional arteriography, i.v. DSA and angioplasty.

The kidney, which is still eliminating the CM several hours after the examination, is regarded as the critical organ in such examinations. The influence of the nonionic CM Ultravist on renal function was examined in various clinical trials. Renal function was not recognizably impaired in any of the patients examined.

The cardiovascular effects of conventional ionic CM are largely attributable to their high osmolality:

- Vasodilatation, reduction of the peripheral resistance and a decrease of blood pressure.
- Hypervolemia.
- Bradycardia in cardioangiography.

Nonionic CM influence the function of the heart and circulation only in exceptional cases.

PROPHYLAXIS AND THERAPY OF SEVERE IODINE-INDUCED HYPERTHYROIDISM

When iodinated CM are administered, a healthy thyroid gland can adjust to an iodine surplus in a host of ways without increasing hormone production.

In a diseased organ, these selfregulating mechanisms can fail to function. In this way, a diagnostic or therapeutic iodine administration can result in severe metabolic dysfunctions such as decompensated hyperthyroidism and thyrotoxic crisis. At special risk are goiter patients (struma) and generally patients with hyperthyroidism. For this reason, iodinated CM should not be applied before hyperthyroidism is excluded.

According to our present state of knowledge, the risk that hyperthyroidism will develop is not diminished by nonionic CM such as Ultravist. The risk of hyperthyroidism is exclusively determined by the iodine and/or iodide contents of the CM. Osmolality and possible chemically toxic properties do not play any role. The renal, water-soluble, ionic and nonionic X-ray CM – as a result of the way they are produced – contain only traces of iodide and very little of the stably chemically bonded iodine is separated off in the organism. Nevertheless, even these small amounts can result in further deteriorating the functioning of a severely damaged thyroid gland (e.g. with manifest hyperthyroidism).

A peculiarity of iodine-induced hyperthyroidism is the fact that deterioration customarily does not occur immediately but weeks or months after the iodine is administered. If diagnostic measures make it essential to use iodinated CM in a patient with hyperthyroidism,

a combined prophylactic treatment of perchlorate and carbimazole (or thiamizole) should be undertaken. The administration of perchlorate (3 x 300 mg daily, from 1–2 days before until 1 week after CM administration) inhibits the absorption of iodine by the thyroid gland; the administration of methimazole simultaneously blocks hormone synthesis (2 x 20 mg thiamizole daily, from 1–2 days before until 2–3 weeks after CM administration).

The longer retention times of biliary CM require a further 3 weeks of treatment with half the dose of thiamizole (carbimazole).

RENAL DAMAGE

Ionic and nonionic contrast media which are used in urography, angiography and computed tomography are eliminated mainly via the kidneys. Isolated cases of diminished kidney function up to and including acute renal failure following intravenous as well as arterial contrast media administration have been described in the literature.

However, the risks related to intravenous administration to patients without obvious risk factors has been, to some extent, exaggerated in the past. In systematic comparison studies [41, 42], it was shown that spontaneous changes in kidney function in patients who had received no contrast media were not significantly less common than in patients receiving contrast media, e.g. for computed tomography.

Renal insufficiency

When ionic CM is administered intravenously in urography to patients with healthy kidneys, deterioration in renal function is hardly ever observed; it is, however,

somewhat more frequent in those with renal insufficiency. Deterioration is defined as an increase of 1 mg/dl in serum creatinine. More recent nonionic CM are well tolerated by the kidneys of patients with reduced renal function – e.g. after administering iopromide intravenously – and demonstrated in several trials no clinically relevant changes in the parameters describing renal tolerance: serum creatinine, creatinine clearance, and urinary protein.

In arteriography, part of the CM can flow directly into the kidneys almost undiluted. Under these conditions, impairment of renal function is more likely, even though nonionic CM have been better tolerated, especially in renal arteriography, than ionic CM.

Plasmocytoma

Disturbed renal function is found in a high percentage of patients with multiple myeloma. Isolated instances of acute renal failure in myeloma patients following urography have been reported in the literature. Almost all of these patients presented additional risk factors prior to treatment, such as severe dehydration and/or sepsis. In addition, almost all of the urographic examinations were conducted with diiodinated CM, which was previously customary. However, in more recent retrospective studies on patients with confirmed multiple myeloma who underwent intravenous urography, no temporal connection could be established between an increase in substances normally contained in the urine and the administration of CM. In the opinion of experts, given adequate hydration and the use of modern CM, plasmocytoma does not represent an a priori contraindication for CM administration. Rather, more recent studies list the principal risk factors for acute renal damage in patients with multiple myeloma as hypercalcemia, dehydration, infections and Bence

Jones proteinuria [73]. In patients with serum creatinine values above 2 mg%, urography should no longer be performed.

Diabetes mellitus

Proteinuria and increase in serum creatinine in a diabetes mellitus patient requiring insulin indicate an advanced case of diabetes glomerular sclerosis. Given CM administration, deterioration in renal function in such a patient must be considered more likely. Acute renal failure in a diabetes mellitus patient occurs as a rule only in the case of severe proteinuria (300 mg/24 h). In this condition, the modified composition of urine tends to precipitate in the presence of CM, a potential cause of tubular blockage.

Prophylaxis

Patients with risk factors in regard to renal tolerance of the contrast medium, i.e. with

- limited renal function and simultaneously
- a long history of insulin-dependent diabetes mel.,
- cardiac insufficiency
- and advanced age,

should not receive high doses of intravascularly administered contrast media. With ultrasound, magnetic resonance imaging and arterial digital subtraction angiography, there is a sufficient number of alternative procedures which can avoid or diminish the use of X-ray contrast media.

The following prophylactic measures are recommended to reduce the risk of renal damage [44]:

- sufficient consumption of liquids
- avoid multiple examinations with X-ray contrast media during periods of only a few days

- discontinuation of medications which could also cause renal damage

A recommendation for medicinal prophylaxis adequately confirmed by clinical studies cannot at present be made [74]. Indications of a prophylactic effect are known primarily for theophylline [75].

PREGNANT PATIENTS

The use of CM during pregnancy has not yet been proven to be harmless although toxicological studies in animals or clinical experience do not indicate any particular risk. Since exposure to radiation should be avoided if at all possible during this period, the potential risks of any X-ray examination must be given careful consideration.

BREAST-FEEDING MOTHERS

Renal CM and i.v. cholegraphic agents hardly enter into a mother's milk. They are barely reabsorbed in breast-feeding so that one can assume that there is no danger to the infant. Even with oral cholecystographic agents the exposure of the infant is minimal.

PHEOCHROMOCYTOMA

In patients with pheochromocytoma, X-ray examinations are often undertaken prior to surgery in order to determine the position, size, and number of tumors. Such examinations are not totally without risk to patients. In angiography, especially in selective CM injection into tumor vessels, a spontaneous release of massive amounts of catecholamine into the blood-

stream can occur, a reaction we are already acquainted with from other situations of stress. This results in a hypertonic crisis. A critical drop in blood pressure represents a much more unusual, but more serious incident. Diagnostic intervention should only be made on pheochromocytoma patients after individually dosed treatment with alpha-adrenergic receptor blockers for a sufficient length of time (10–14 days).

SICKLE-CELL ANEMIA

In sickle-cell anemia patients, some erythrocytes contain the abnormal hemoglobin S. If O_2 pressure is lowered or blood osmolality is raised, HbS-containing blood corpuscles take on an inelastic, stretched-out form. These erythrocytes can no longer pass through capillaries as easily, which can lead to stasis and to different forms of organ damage.

Administering CM to such patients is not without its problems. The greatest risk is produced by intra-arterial CM injection, especially in high doses, as is the case in cerebral and cardiac arteriography. In in vitro studies, the effect of ionic and nonionic CM were comparatively examined in terms of sickle-shaped changes in erythrocytes. It turned out that nonionic CM cause such changes significantly less often.

DRUGS AND MEASURES FOR THE TREATMENT OF A CONTRAST MEDIUM REACTION

A major prerequisite for working with CM is a constant preparedness for the treatment of CM reactions. This includes the availability of trained medical personnel, the necessary equipment and appropriate drugs. In Table 21 suggestions for the treatment of CM reactions are offered. Most of these charts also mention suitable drugs which should always be ready to hand. A corresponding compilation was published by Bush and Swanson [45]. CM reactions are very rare particularly with the new, nonionic preparations; however, the need to be prepared for their treatment should never be neglected. One easily overlooked point to note is the expiry date on the preparations to be used for the treatment of such reactions.

Notes on the prophylaxis and therapy of X-ray contrast medium reactions

A Risk factors and prophylactic measures on use of X-ray contrast media

Compiled by:
Prof. Dr. K. Steinbereithner,
University Clinic for Anesthesia and
General Intensive Care,
Spitalgasse 23, 1090 Vienna

and
Prof. Dr. M. Reiser,
Klinikum Grosshadern, Munich University,
Institute for Radiodiagnosis,
Marchioninistr. 15, 81377 Munich

Preconditions for an intravascular injection of contrast medium are:

- Explanation to the patient about the method and risks
- Anxiety-free examination atmosphere
- Establishment and prophylaxis of risks
- Adequate fluid intake
- Availability of equipment and drugs for the treatment of incidents
- Alarm plan
- Experience in cardiopulmonary resuscitation
- Availability of venous access (at least in high-risk patients)
- Patient in the prone position whenever possible

Risk factors

- Known hypersensitivity to X-ray contrast media
- Allergic diathesis – atopia (eczema, urticaria, neurodermatitis, asthma, food allergy, pollinosis)
- Hyperthyroidism, nodular goiter
- Severe cardiovascular disease (heart failure, coronary sclerosis, recent infarction, pronounced arrhythmias, severe hypertension etc.)
- Reduced general condition, exsiccosis
- Severe impairment of kidney function
- Severe impairment of liver function
- Severe diabetes mellitus
- Severe pulmonary disease (respiratory insufficiency, pulmonary hypertension, pulmonary embolism etc.)
- Cerebral injury (fresh cerebrovascular insult, convulsions, cerebrocranial trauma)
- Paraproteinemias (Waldenström's disease, plasmocytoma etc.)
- Pheochromocytoma (risk of hypertensive crises)
- Age more than 65 years (multimorbidity), babies, infants
- Excessive anxiousness
- Reexposure to contrast medium at short intervals
- Beta-blocker medication: bronchospasm, tendency towards therapy-resistant bradycardia possible
- Long-term administration of calcium antagonists with tendency towards bradycardia and/or vasodilatation
- Chemotherapy with interleukin-2 and/or interferon
- Treatment with biguanide-type antidiabetics (impairment of kidney function, risk of lactate acidosis)
- Sickle cell anemia

Prophylactic measures in high-risk patients

- Nil by mouth
- Use nonionic contrast media, low-dosed
- Premedication with antihistamines:
  H1 beta-blocker: clemastine 2–4 mg (1–2 amp. Tavegil®) or dimetindene maleate 4–8 mg (1–2 am. Fenistil®) slowly i.v. 10–15 min. before contrast medium administration
  H2-blocker: cimetidine 200–400 mg (1–2 amp. Tagamet®) slowly i.v. or as short infusion in 50 ml 0.9% NaCl solution
- Premedication with glucocorticoids
  orally: methylprednisolone (e.g. Urbason® 40 mg 1 tablet each time) 24 h, 12 h and 2 h before contrast medium administration
  i.v.: prednisolone (Soludecortin®) or methylprednisolone (Urbason® solubile)
  250 mg at least 30 min., better 2 h before contrast medium administration
- Stabilization of the cardiovascular system
- Normalization of fluid and electrolyte balance
- Avoidance of potentially nephrotoxic drugs (e.g. nonsteroidal antirheumatics, aminoglycosides, amphotericin B, cisplatinum, cyclosporin, metformin)
- Possibly sedation with diazepam (Valium®) 10 mg p.o. or midazolam (Dormicum®) 7.5–15 mg p.o. or 2.5–5 mg slowly i.v. Caution: respiratory depression
- In thyroid autonomy: sodium perchlorate (Irenat®) before (40 drops), 2 h after CM administration (20 drops) and after 1 week (3 x 15 drops daily)
- In hyperthyroidism (X-ray contrast medium only in vital indication): additionally 20 mg thiamazol (Favistan®) daily (1–2 weeks)
- In pheochromocytoma patients to avoid hypertensive crises: administration of alpha-receptor blockers, e.g. urapidil (Ebrantil®)

Monitoring (ECG, pulse, blood pressure, possibly pulse oxymetry) is advisable throughout the entire examination in patients at increased risk

Table 21. Recommendations for treating contrast media reactions

B Measures on contrast medium reactions

Compiled by:
Prof. Dr. K. Steinbereithner,
University Clinic for Anesthesia and
General Intensive Care,
Spitalgasse 23, 1090 Vienna

and
Prof. Dr. M. Reiser,
Klinikum Grosshadern, Munich University,
Institute for Radiodiagnosis,
Marchioninistr. 15, 81377 Munich

SEVERITY GRADE I

Sneezing, urge to cough, yawning, erythema, slight fever, nausea, retching, chill

- Discontinue injection
- Assure venous access
- Possibly antiemetics, e.g. triflupromazine (Psyquil®), ondansterone (Zoftran®)

Flush, itching, urticaria, blepharedema

- H_1 and H_2 receptor blockers: dimetindene maleate 8–12 mg (2–3 amp. Fenistil®) clemastine 4–6 mg (2–3 amp Tavegil®) cimetidine 400 mg (2 amp. Tagamet®) slowly i.v.
- If necessary, glucocorticoids i.v. (corresponding to 250 mg prednisolone)

Shock
- **Tachycardia**
- **Massive drop in blood pressure**

SEVERITY GRADE II

Hypotension

- Lay patient flat, ensure fresh air
- Oxygen administration (tube or face mask)
- Rapid infusion of a plasma substitute and/or of Ringer's lactate (500–1000 ml)

also:
Bradycardia (vasovagal reaction)

- Atropine 0.5–3 mg i.v. possibly orciprenaline 0.25–0.5 mg 1/2–1 amp. Alupent slowly i.v.

Dyspnea
Spastic coughing

- 1–2 puffs of a broncholytic (dosing aerosol)
- Aminophylline 0.24 g i.v.
- Glucocorticoids i.v. (corresponding to 250–500 mg prednisolone), effective only after 5–10 min.
- Oxygen (via face mask) (half-)sitting position
- Possibly sedation with diazepam 5 mg i.v. (Valium®)

Every patient should always be kept under supervision for at least 30 min. after contrast medium administration, since around 90% of all reactions occur within this period of time.
High-risk patients, on the other hand, should be monitored for a longer period.
Late reactions (including skin reactions, cardiovascular disorders) can occur in rare cases.
Serious incidents require supervision and therapy in intensive care.

Table 21. Continuation

SEVERITY GRADE III

- Start progress record
- Summon emergency team, anesthesia department or emergency doctor
- Oxygen (via face mask)
- Rapid infusion of at least 1500–2000 ml Ringer's lactate or plasma substitute
- Adrenalin-Medihaler®
  Dosing aerosol 1–2 puffs
- Epinephrine 0.1–0.3 mg i.v. with monitoring of heart function (Caution: arrhythmia) every 10–15 min.
  Dosage according to effect:
  Rising to total dose 1.0 mg if necessary (e.g. 1 amp. Suprarenin 1:1000 diluted to 10 ml, i.e. 1 ml. corresponds to 0.1 mg epinephrine)
  If no intravenous access, epinephrine administration (with decreasing efficacy) if necessary intrabronchially in doubled dose via a tube, in the subglottic venous plexus, i.m. or even i.c.
- H_1 and H_2 receptor blockers as under Grade I
- Glucorticoids i.v. (corresponding to 1000 mg prednisolone), effective only after 5–10 min.
- Dopamine (2 amps. of 200 mg) to 250 ml infusion: 15–30 drops per min., dosage according to effect
- In refractory hypotension possibly
- Change to norepinephrine (5–10 mg to 250 ml infusion)
  Dosage according to effect or 1 mg/10 ml; 0.5–1.0 ml i.v., further dosage titrated according to effect

Broncho-(laryngo-) spasm, stridor, asthma attack

- Sitting position
- Oxygen (via face mask)
- Aminophylline 0.24 g i.v.
- Adrenalin-Medihaler® dosing aerosol 1–2 puffs or beta-2 mimeticas dosing aerosol (e.g. Sultanol®, Berotec®)
- Epinephrine 0.1–0.3 mg i.v. (e.g. Suprarenin®) 1:1000 diluted to 10 ml, possibly rising to total dose 1.0 mg
- H_1 and H_2 receptor blockers as under Grade I
- Glucocorticoids i.v. (corresponding to 250–1000 mg prednisolone), effective only after 5–10 min.
- Possibly diazepam 5 mg i.v. (Valium®) for sedation; intubation if necessary

Edema of the glottis

- Possibly intubation
  or
- oxygen after puncture of the cone with a thick needle, coniotomy if necessary

Pulmonary edema

- Possibly intubation
  and
- positive pressure ventilation with oxygen, furosemide 40 mg i.v. (Lasix®)
- Possibly morphine 0.01–0.015 g slowly i.v.

Convulsions

- Diazepam 5–10 mg i.v. (Valium®)

SEVERITY GRADE IV

Circulatory and respiratory standstill

- Immediate institution of cardiopulmonary resuscitation (cardiac pressure massage and ventilation)

Telephone: Emergency ambulance:

Telephone: Anesthesia department:

SPECIAL CHARACTERISTICS OF THE CONTRAST MEDIA FOR MAGNETIC RESONANCE IMAGING

MECHANISM OF ACTION

Contrasts in an X-ray film or X-ray computed tomogram are caused by the differing absorption of the rays as they pass through structures in the body. It is easy to calculate the quantity of a contrast medium in the path of the rays, or the contrast medium concentration in a given volume (CT) from the ray absorption, if the absorption in the same region is known before contrast medium administration.

The physical principle of magnetic resonance imaging is completely different.

- Magnetic fields and radio waves are used instead of X-rays.
- Instead of all matter, e.g. in one organ, only one type of atom is visualized (usually hydrogen = ^1H = proton).
- The brightness in one image point is dependent mainly, aside from the concentration of the element in question, on its relaxation times T_1 and T_2, the movement, e.g. with the bloodstream, the adjustment of the apparatus parameters and various other factors.

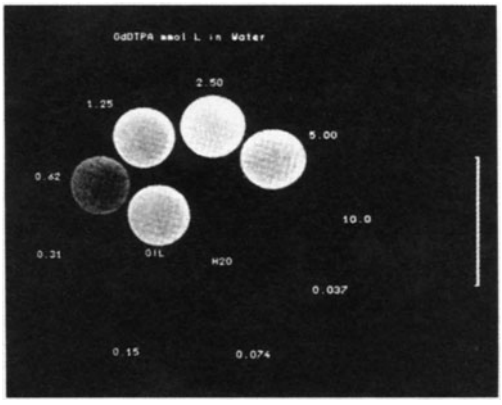


Fig. 24. Signal intensity of aqueous solutions with various concentrations of gadolinium-DTPA in magnetic resonance imaging (SE). In the middle a tube with oil (light) and with water (dark). The numbers on the edge show the millimolar concentrations of gadolinium-DTPA (mmol · l^{-1} in water). The maximum brightness is observed at 2.5 mmol/l. At 10 mmol/l, the relaxation times are so short that no signal is received

Almost all of the contrast media tested or used in magnetic resonance imaging [45, 46] cannot be seen in the image. However, they influence the visibility of the protons in that either these protons emit more signals during the measuring time (mainly shortening the relaxation time T_1) or that they emit less intense signals (mainly shortening of the relaxation time T_2). Because both effects al-

ways occur simultaneously, there is a more or less complex dependency of the image brightness on the contrast medium concentrations, depending on the type of contrast medium (figs. 24, 25). However, only a signal increase (bright image) in tissues is normally achieved with the intravascular contrast media in use today; in the kidneys, the contrast media concentrations can become so high that signal losses can actually occur.

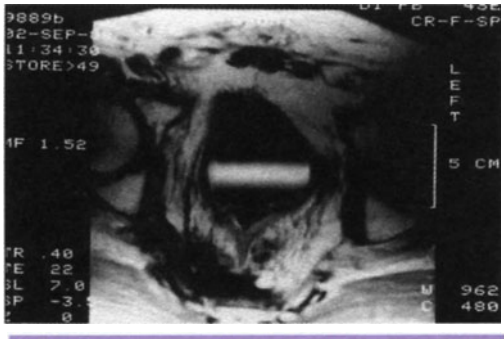


Fig. 25. The same phenomenon as in fig. 24 can be observed in patients. The urine normally has a low signal intensity (long T_1), upper part of the bladder. Gadolinium-DTPA is concentrated in the kidneys to a degree that no signal is received due to the too-short relaxation times (lower part of the bladder; because of the greater specific weight, the urine formed after the CM injection does not mix with that already present in the bladder). In the middle layer there is a zone of optimum CM concentration and maximum signal intensity

Ultimately, today's intravascular contrast media are more effective the longer the native relaxation times are in the body regions concerned (table 22). With long initial relaxation times, as they occur in liquids (urine, gastrointestinal contents, cerebrospinal fluid, interstitial fluid accumulations) very small quantities of contrast medium are sufficient to cause significant effects. If the relaxation times are already short (liver), the contrast medium concentration must be increased, and special measuring sequences (e.g. with very short echo times) must be used in order to register a further abbreviation of the relaxation times.

The local contrast medium concentration is determined by pharmacokinetics in the same manner as X-ray contrast media. It is directly proportional to the applied dosage.

Concentration Gd-DTPA (mmol/l)	T_1 msec	T_2 msec
0	3700	2400
0.21	600	473
0.83	300	249
1.7	150	116
3.6	70	56

Table 22. Influence of Gd-DTPA on the relaxation times T_1 and T_2 of water at 0.47 Tesla and 20 MHz

STRUCTURE AND PHARMACOLOGICAL CHARACTERISTICS

The most common contrast medium for magnetic resonance imaging is Magnevist®, which contains the

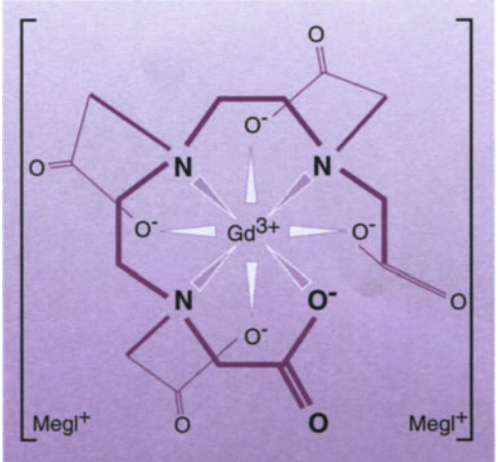
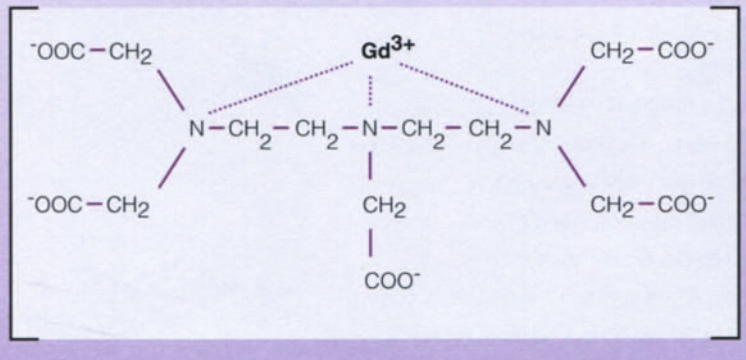


Fig. 26a. Model of gadolinium-DTPA

active ingredient gadolinium-DTPA (fig. 26). The principle of action is the paramagnetic gadolinium ion (table 23). Gadolinium is an element of the rare earths group. It is characterized by especially strong paramagnetic properties and it influences the relaxation time T_1 (and T_2) more strongly than other metal ions.

Gadolinium ions are, like many other metal ions, eliminated only slowly and they are too toxic by themselves to be used as a contrast medium. Therefore, Magnevist® contains the DTPA-complex of gadolinium in which the metal ion



Stability constant ~ 10^{22} - 10^{23}

Molecular weight 550 (acid)

Water solubility > 1 mol/l

Fig. 26b. Structural formula of gadolinium-DTPA

is firmly bound and which is not recognized by the body as a heavy metal and is practically not exchanged for other metal ions [49]. The pharmacokinetics of the gadolinium are completely changed by complex formation. It remains in the extracellular space after intravascular injection, does not bind with proteins, does not pass the intact blood-brain barrier and is eliminated rapidly and completely through glomerular filtration.

Practically no side-effects have been determined in animal experiments using the clinically applied dosages of 0.1 to 0.3 mmol/kg, even during rapid i.v. injection. About the only effects noted in the standard high overdose tests during the toxicological investigations were osmotic effects which have no meaning in the normal dosage range. Gd-DTPA is also surprisingly well-tolerated after injection into the cerebrospinal fluid (which has, however, not been approved by the health authorities and for which purpose Magnevist® is unsuitable in its undiluted form!).

Besides Magnevist® a range of contrast media containing gadolinium have been developed. In these, other complex-forming agents are being employed; however, the diagnostic effectiveness is the same. Gadovist® and Gadoteridol, for example, are neutral macrocyclic complexes of the trivalent gadolinium. The lower osmolality of these contrast agents permits the use of higher doses such as are required in MR angiography or perfusion studies. Gadovist is, moreover, the first MR contrast agent to be offered in the 1 molar concentration. The advantages of the higher concentrations are a sharper bolus for dynamic examinations and the

Gadolinium
◆ Element of the rare earth group
◆ 7 single electrons
◆ always trivalent: Gd^{3+}
◆ toxic as a free ion (compare to iodide)
◆ forms stable complexes, especially with DTPA
◆ well tolerated as a complex (compared to iodinated X-ray contrast media)

Table 23. Characteristics of gadolinium which indicate its suitability as the active ingredient for contrast media for magnetic resonance imaging

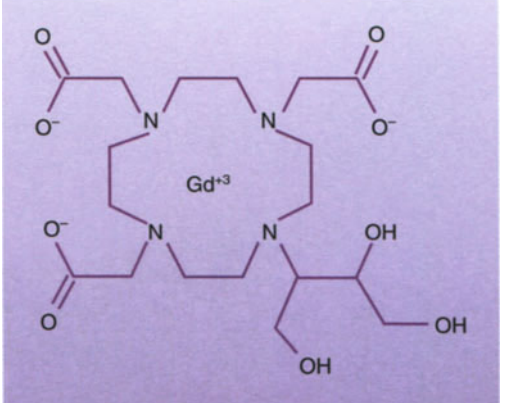


Fig. 27. Structural formula of gadobutrol

	Effect	Pharmacokinetics	Concentration (ready for use)	Preparation for use	Formulation
Dotarem® Gd-Dota/Megl. Gadoterate	T_1	urographic CM	0.5 molar	ready for use	clear solution
Pro Hance® Gd-DO3A-HP Gadoteridol	T_1	urographic CM	0.5 molar	ready for use	clear solution
Omniscan® Gd-DTPA-BMA Gadodiamide	T_1	urographic CM	0.5 molar	ready for use	clear solution
Gadovist® Gd-DO3A-butrol Gadobutrol	T_1	urographic CM	0.5 molar 1.0 molar	ready for use	clear solution
Magnevist® enteral Gd-DTPA Gadopentetate	T_1	gastrointestinal	1 mmolar	dilute	clear solution
Abdoscan® Ferristen	T_2	gastrointestinal	23.4 mg Fe/200 ml	suspend granules in water	viscous suspension
Lumirem® Ferumoxsilium	T_2	gastrointestinal	52.5 mg Fe/300 ml	ready for use	suspension
Endorem® (= Feridex®)	T_2	RES (liver, spleen)	11.2 mg Fe/ml	dilute	suspension
Teslascan® Mn-DPDP Mangafodipir	T_1	hepatocytes (pancreas, heart) manganese ions	0.01 mmol/ml	dilute	clear solution

Table 24. Commercial preparations excluding Magnevist®

smaller volume administered for higher dosages. The concentration of gadolinium in the 1 molar solution is 157 mg/ml (fig. 27).

The first liver and spleen-specific contrast agent to be made available is Endorem® (called Feridex® in the USA) (table 24). The principle of its action are superparamagnetic iron oxide particles measuring about 100 nm, which are stabilized by a dextran coating. After intravenous injection the magnetite particles accumulate in the RES of the liver and spleen. Metastases

Osmolality mosm/kg H_2O	Viscosity mPa · s 37° C [log K]	Thermic stability constant	Additive(s)	Kinetic stability [t ½]	Effective stability constant at pH 7.4
1 350	1.82	25.8	meglumine	one month	18.8
630	1.35	23.8	calteridol Ca, trometamol	3 h	17.1
798	1.47	16.9		30 sec.	14.9
557 1 603	1.41 4.96	21.8	Ca, Na butrol, trometamol	24.2 h	~ 15.6
–	–	–	DTPA, citrate, mannitol	–	–
–	–	–	several tumefacients, polystyrene sulfate	–	–
–	–	–	silane, preservatives, sorbitol flavorings	–	–
340	1.3 (20° C)	–	dextran, citrate, mannitol	–	–
290	–	–		–	–

and most tumors contain no or markedly fewer macrophages and so do not take up the contrast medium. Endorem®'s powerful T_2-effect extinguishes the signal [76]. Marketing authorization has been applied for a preparation with a comparable principle of action called Resovist®. It is easier to handle, is better tolerated and has quicker and more potent efficacy.

Teslascan®, an unstable complex of manganese^{2+}, is a further liver-specific MR contrast agent which has been granted marketing authorization. The

	Effect	Pharmacokinetics	Concentration (ready for use)	Preparation for use
Optimark® Gadoversetamide Gd-DTPA-BMEA		urographic CM	0.5 mol/l	ready for use
Multi Hance® Gadobenate dimeglumine (Gd-BOPTA)	T_1	urographic CM	0.5 mol/l 0.25 mol/l	ready for use
Resovist® Ferucarbotran	T_2	RES/liver	0.5 mol Fe/l	ready for use
Eovist® Gadoxetic acid (Gd-EOB-DTPA)	T_1	50% urographic 50% biliary	0.25 mol/l	ready for use
Sinerem® (= Combidex) Ferumoxtran	T_1/T_2	lymphatic CM, blood-pool CM, liver		dilute

Table 25. Developmental preparations undergoing clinical trials

manganese ions accumulate mainly in the healthy liver parenchyma after intravenous injection and induce a persistent shortening of the relaxation time T_1 and signal enhancement. Gadolinium-EOB-DTPA (Eovist®) is a stable hepatocyte-specific complex of which about 50% is subject to biliary elimination and which is currently at an advanced stage of clinical investigation (table 25).

PHARMACEUTICAL PRODUCT QUALITY

Magnevist® is a concentrated aqueous solution of the dimeglumine salt of gadolinium-diethylene-triamine-pentaacetic acid (= dimeglumine gadopentetate = Gd-DTPA dimegl.) with an addition of 1.02 mg/ml DTPA (table 26). The solution is clear and watery and is in this regard similar to the X-ray contrast media. The relatively high osmolality is unimportant for intravenous administration as Magnevist® can be given in much lower doses as compared to X-ray contrast media.

Formulation	Osmolality mosm/kg H_2O	Viscosity mP · s 37° C	Thermic stability constant [log K]	Additive(s)
clear solution				
clear solution	750	1.6		
suspension	333	1.03		lactate, mannitol, sodium hydroxide
clear solution	884	1.23	23.46	trometamol, Ca-EOB-DTPA
suspension				

The following are decisive for the quality of the contrast medium:

1. The purity of the gadolinium: 99.999%

2. The purity of the complex-forming agent DTPA, especially in regard to the contamination with chemically related substances which, however, only bind gadolinium less strongly.

3. A small excess quantity of free DTPA, which guarantees a complete binding of the gadolinium ions under unfavorable conditions.

The pH value of Magnevist® is about 7. The stability of the complex is very high in the physiological pH-range and cannot be completely guaranteed below pH 2.5.

The solution exhibits two absorption maximums in the UV range, one at 273 nm and a weaker at 276 nm (measurement of a ca. 50 mmol solution, therefore very low detection sensitivity as compared to UV measurement of triiodinated X-ray contrast media).

Gadolinium-DTPA, dimeglumine salt; molecular weight		938
Contrast media concentration	(mg/ml) (mol/l)	469 0.5
Meglumine-DTPA as a complexing agent surplus max:	(mg/ml)	1.02
Viscosity	(mPa • s, 37°C) (mPa • s, 20°C)	2.9 4.9
Osmolality	(osm/kg H_2O)	1.96
pH		6.5–8.0
Density	(kg/l, 20°C)	1.207
Relaxivity	(T_1 l/mmol sec, 0.47 T, 39°C) (T_2 l/mmol sec, 0.47 T, 39°C)	3.84 ± 0.04 4.34 ± 0.06
Clear, colorless solution		

Table 26. Magnevist®, composition of the solution

The following must be observed when handling Magnevist:

- All safety measures for X-ray contrast media apply (see page 48ff).
- Magnevist® is rather more stable than standard X-ray contrast media, i.e., it is less sensitive to the influences of heat (up to 120° C) and light.
- The formation of crystals has not been observed, even after storage at very low temperatures.
- Magnevist® has a low viscosity. Warming the solution to reduce the viscosity is, as a rule, not necessary.
- Undiluted Magnevist® inhibits the growth of microorganisms (fig. 28). It is therefore less sensitive to microbial contamination than nonionic X-ray contrast media.
- Microbial contamination of the solution need not be expected on aseptic withdrawal from the same

contrast medium container for use in a number of patients [77].

ADMINISTRATION

In many respects, the administration of Magnevist® in magnetic resonance imaging is similar to that of X-ray contrast media in computed tomography.

- Intravenous injection.
- Injection speed can be chosen as needed; for dynamic examinations a rapid bolus injection is also possible.
- The dosage is generally 0.1 mmol gadolinium-DTPA/kg body weight or 0.2 ml Magnevist®/kg. Good results are achieved in adults with the injection of 20 ml (contents of one injection bottle). The effect can be increased by doubling the dosage to 0.2 mmol/kg body weight; for central nervous system diagnostics, this dosage can also be reached by injecting 0.1 mmol/kg within 30 minutes after the first injection.
- As opposed to computed tomography, no contrast medium is required to delineate the blood vessels in magnetic resonance imaging, as the flowing blood is delineated from the surrounding tissue by its low signal intensity (dark). Using special flash sequences in 3D-MR-angiography, Magnevist® makes a somewhat larger pulse angle possible by reducing the relaxation time in the blood, which leads to better image quality. This applies especially in the brain, as the contrast

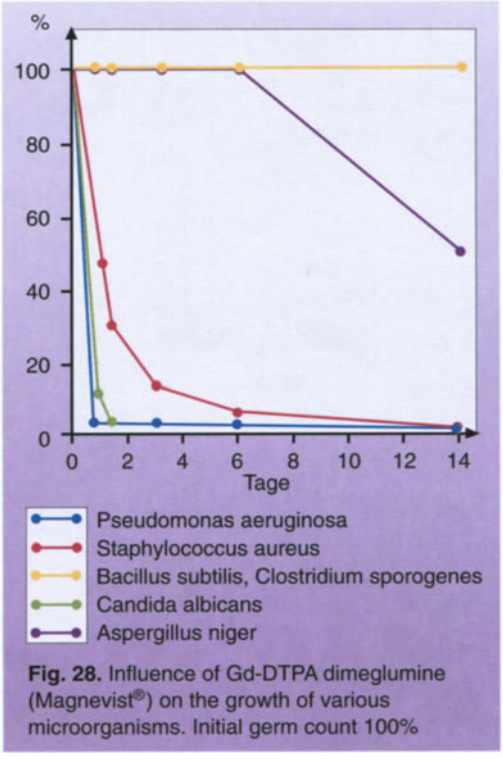


Fig. 28. Influence of Gd-DTPA dimeglumine (Magnevist®) on the growth of various microorganisms. Initial germ count 100%

medium is restricted to the blood vessels because of the blood-brain barrier.

- In the central nervous system, all areas of increased permeability of the blood-brain barrier are prone to signal increases through the administration of Magnevist® (table 27).
- In the rest of the body, areas with
  - rapid perfusion
  - a high proportion of interstitial fluid and
  - relatively long relaxation times before contrast medium administration are especially prone to an increase in their signal intensity (table 28).
- In the kidneys and urinary tract, contrast medium concentrations may increase to a point where signal losses occur.

Other applications of gadolinium-DTPA for the imaging of body cavities definitely require special preparations. The 0.5 molar solution for intravenous injection is not suitable. The same applies to the 0.5 and 1.0 molar Gadovist® preparations.

Signal changes in the case of disturbances or lack of the blood-brain barrier, e.g.
◆ metastases
◆ meningiomas
◆ glioblastomas
◆ acoustic neurinomas
◆ pituitary adenomas
◆ inflammations
◆ infarctions (time window)
◆ MS (active plaques)
◆ plexus chorioidei
No or only minimal influence on signal intensity, e.g.
◆ cerebrospinal fluid
◆ healthy brain parenchyma
◆ astrocytomas

Table 27. Magnevist® in the central nervous system

CONTRAST MEDIA FOR THE GASTROINTESTINAL TRACT

Contrast media can, in a similar manner to computed tomography, help to greatly improve the delineation of the lumen of the gastrointestinal tract from the surrounding tissues. The prerequisite for the use of paramagnetic substances, other than optimum contrast medium concentrations, is the presence of water. For this reason, a special preparation of Magnevist® was developed which contains a gadolinium-DTPA con-

None or very little	Moderate	Significant
Muscle	Liver	Kidney (medulla > cortex)
Fat	Pancreas	Urine
Bone	Gastrointestinal mucosa	Nasal mucosa
Bile ducts, gall bladder		Blood (depending on flow and measuring mode)
Cysts		Operation scars Inflammations Infarctions: liver, spleen Heart: acute ischemia, infarction Tumors: Liver, hypernephroid, lung, breast, pelvis, bone, muscle connective tissue

Table 28. Influence of Magnevist® on signal intensity outside of the central nervous system

centration of only 1 mmol, with the addition of mannitol to limit the water absorption from the gastrointestinal tract, and a buffer to stabilize the gadolinium-DTPA in the stomach (Magnevist® enteral). Two other preparations are approved for the same purpose: Abdoscan® and Lumirem®. Both contain magnetites which reduce the signal intensity.

CONTRAST MEDIA FOR OTHER BODY CAVITIES

For special diagnostic problems, the use of contrast media to increase the signal intensity of body fluids, e.g. as performed in X-ray diagnostics using arthrography or myelography, could be beneficial. Currently, there is no approved preparation for this purpose.

As a general rule, a Magnevist® solution diluted to 2 mmol/liter is suitable, if a sufficient part of the volume being represented is replaced. With greater dilutions, a 10 mmol solution must be used. This type of

dilution must be performed with physiological saline solution or another tolerable phosphate-free isotonic medium, because Magnevist® is definitely hypotonic in low concentrations. Phosphates must be avoided as they form very insoluble salts with gadolinium.

- 1 ml Magnevist® + 249 ml physiological NaCl = 2 mmol gadolinium-DTPA/liter
- 1 ml Magnevist® + 49 ml physiological NaCl = 10 mmol gadolinium-DTPA/liter

The sterility of the preparation must be guaranteed during administration in body cavities.

SPECIAL HANDLING CHARACTERISTICS

The intravenous administration of Magnevist® can be performed in the same manner as that of X-ray contrast media in computed tomography. However, the following must be observed:

- The effect of paramagnetic contrast media such as Magnevist® is not proportional to the dosage but increases rapidly at first, then reaches a plateau and can, under certain conditions (kidneys, urinary tract, certain measuring sequences) also decrease.
- It is not necessary to calculate the administered dosage of Magnevist® too exactly; there is a broad dosage range with generally good tolerance.
- Magnevist® has, despite lower dosages, greater efficacy than X-ray contrast media in computed tomography. Therefore, it can be useful in cases where sufficient contrast increase cannot be achieved with X-ray contrast media.
- The creation of a preparation for contrasting the gastrointestinal tract cannot be performed through simple dilution of Magnevist®.

- Dilution and mixing of Magnevist® with other solutions, which contain salts or complex-forming agents other than NaCl, glucose or mannitol (i.e. phosphates, electrolyte solutions, iron preparations) must not be performed in order to avoid the risk of ion exchange in the chelate.
- Magnevist® is very well tolerated and can be injected as a concentrated solution without discomfort. The relatively high osmolality may be undesirable in small children or may lead to temporary pain during perivascular injection (e.g. with uncertain positioning of the injection cannula). This can be avoided by diluting Magnevist® with water for injection (or physiological saline solution):

Osmolality of diluted Magnevist® solutions (mosm/kg H_2O)

Dilution	Dilution medium	
	water for injections	physiol. NaCl
1 + 1	770	940
1 + 4	270	520

A dilution of Magnevist® at a ratio of 20 ml + 20 ml water will significantly reduce the osmolality, and in a dilution of 20 ml Magnevist® to 100 ml final volume, the osmolality lies significantly below that of today's commonly used nonionic X-ray contrast media.

INFLUENCE ON LABORATORY TESTS

The influence of gadolinium-DTPA on laboratory tests has been investigated [47]. It was shown that Magnevist®, through the small surplus of free complex-forming

agents, binds metal ions which should either be measured or are used as reagents for the measurement of other substances. However, concentrations in serum sufficient to disturb laboratory tests could hardly be achieved (with the single exception of copper determination).

- None of 12 various tests for serum enzymes was disturbed.
- Protein determination with biuret. A disturbance of the reaction is possible (values too low), but only in urine up to about 4 hours after administration of the contrast medium.
- Mercurimetric chloride determination. Too high values have been found but only in urine up to about 4 hours after administration of the contrast medium.

Copper

Too low values have been found. Measurements should be performed at the earliest 24 hours after Magnevist® administration.

Calcium

With high contrast medium concentrations, which are rarely achieved in vivo, slightly reduced calcium values can be expected.

Iron

Serum iron determination with complexometric methods (e.g. bathophenanthrolin) can result in too low values up to 24 hours after contrast medium administration.

After injection of Magnevist® in high dosages, occasionally serum iron and bilirubin values may increase; blood for the measurement of these sub-

stances should therefore be taken no sooner than 24 hours after contrast medium injection.

INTERACTION WITH MEDICATIONS

At this time, there are no known interactions with medications. However, an influence of Magnevist® on the distribution of gallium-67 was noted [48]. It must be assumed that the small quantities of the free complexing agent in Magnevist® could influence the distribution of radio isotopes in the body in a manner similar to the influence on laboratory tests. This would be of importance during the use of radioactive isotopes for therapeutic reasons.

Because of the rapid elimination of Magnevist® and also the free DTPA, such an influence should only be expected up to a maximum of 24 hours after administration.

RISKS RELATED TO MAGNEVIST® USE

In clinical trials and since its introduction to the market in 1988, Magnevist® has proven itself as a contrast medium with a surprisingly low incidence of side-effects (table 29). However, it must be remembered that it can cause the same side-effects as iodinated X-ray contrast media after intravenous injection, with the exception of the influence on the thyroid gland. The occurrence rate of general reactions to gadolinium-containing contrast media is only 1–2%; severe

Symptoms	Number	Frequency
Nausea, vomiting	57	0.42%
Warmth, pain at injection site	55	0.41%
Headache	35	0.26%
Paresthesia	18	0.13%
Dizziness	13	0.10%
Focal cramps	2	0.01%
Urticaria	4	0.03%
Other allergic type skin reactions	10	0.07%
Allergic type mucous membrane reactions	7	0.05%
Flush	8	0.06%
Cardiovascular reactions	5	0.04%
Tachycardia, arrhythmia	3	0.02%
Other symptoms	20	0.15%

Table 29 Side-effects following the administration of Magnevist®: 196 of 13,439 (1.46%) patients with 237 symptoms

systemic anaphylactoid reactions are rare. A severe reaction was observed after every 350,000th injection; asthma appears to be a risk factor [78, 79].

A comparative study revealed that up to a dose of 0.4 mmol/kg gadolinium-containing MR contrast media are better tolerated by the kidneys than X-ray contrast media at the doses normally used in computer tomography [80].

Magnevist® is eliminated almost exclusively via the kidneys. Administration in patients with strongly diminished renal function should therefore be carefully considered in relation to the expected benefits.

Magnevist®, just as iodinated X-ray contrast media and creatinine, can be removed from the body through dialysis. Dialysis should, as a precaution, be performed as soon as possible after contrast medium administration.

No indications of embryotoxic or teratogenic effects of Magnevist® were found in animal experiments; on the other hand, in patients the tolerance during pregnancy has not yet been proven.

COMPARISON WITH X-RAY CONTRAST MEDIA

Despite larger differences in physics and chemistry, the effect of Magnevist® in magnetic resonance imaging is similar to that of X-ray contrast media in computed tomography. Tables 30 and 31 contain a comparison of a few of the characteristics. Of interest are the strong efficacy and the surprisingly good tolerance. Dimeglumine gadolinium-DTPA is a salt. The tolerance is, however, at least as good as, possibly even better than, the tolerance of nonionic X-ray contrast media.

	Magnevist®/MRI	Nonionic X-ray contrast media/CT
Contrasting principle	Shortening of relaxation times	X-ray absorption
Image brightness increase	Dependent on ◆ CM concentration (with optimum concentration) ◆ measuring mode ◆ CM distribution in tissue ◆ native relaxation times etc.	Dependent on ◆ iodine concentration
Pharmacokinetics	Extracellular distribution No penetration of blood-brain barrier Elimination through glomerular filtration	Identical
Dosage	10–40 ml = 0.8–3.1 g gadolinium	50–300 ml = 15–110 g iodine
Indications	Focal and inflammatory diseases of the central nervous system (blood-brain barrier disturbances) Perfusion Inflammations Scars Soft-tissue tumors Bone tumors	Blood Focal and inflammatory diseases of the central nervous system (blood-brain barrier disturbances) Perfusion Scars Tumors Kidneys and urinary tract
Frequency of side-effects	ca. 1%	ca. 3%

Table 30 Comparison of various characteristics of Magnevist® and nonionic X-ray contrast media

Symptoms	Nonionic RCM*	Magnevist®**	Ratio RCM/Magnevist®
Nausea, vomiting	1.40%	0.42%	3.3
Warmth, pain at injection site	0.97%	0.41%	2.4
Allergic skin reactions	0.92%	0.104%	8.8
Allergic mucous membrane reactions	0.41%	0.052%	8.0
Flush	0.16%	0.059%	2.7

* Results from 163,386 i.v. administrations (The Japanese Committee on Safety of Contrast Media)
** Results of 13,439 i.v. administrations of Magnevist® (Gd-DTPA)

Table 31. Side-effects following the administration of Magnevist® and nonionic X-ray contrast media

SPECIAL CHARACTERISTICS OF THE CONTRAST MEDIA FOR ULTRASOUND

The medical-diagnostic use of ultrasound began in the 1950s. The technology has undergone constant development ranging from the imaging of the reflected pulse along a line emanating from the transducer (A mode) to the 2-dimensional image of a pulse reflection in gray-scale (B mode) via the representation of the speed of movement and direction of reflected structures (Doppler) using the altered frequency of the reflected pulse to many other parameters resulting from the interaction of the pulse and the living organism.

Ultrasound diagnostics differs from other imaging techniques in medicine in the following aspects:

- Information from within the body corresponding to the reflection and diffraction of the ultrasound
- Sectional images from any direction with a movable transducer and with micro-transducers from inside the body
- Immediate image display with representation of current movements and processes
- Measurement of the speed of the bloodstream through the Doppler effect, integration of this information into an anatomical image (color Doppler image)
- The spatial resolution is dependent on the sound frequency (table 32): high frequency means good resolution and small penetration depth; low frequency means less resolution and greater penetration depth
- Disturbance through gas (lung, intestines) and bones

Frequency (MHz)	Half value depth (mm)	Axial resolution (mm)
1	30	1.5
2.25	13	0.7
3.5	9	0.4
5	6	0.3
7.5	4	0.2
10	3	0.2

Table 32. Dependency of penetration depth and axial resolution on the frequency in soft tissue [50]

CONTRAST MEDIA AND THEIR MECHANISMS OF ACTION

The development of ultrasound for medical diagnostics began in the 1950s, and the first contrasting agents were described in the late 1960s. From a number of very different substances and preparations (table 33), the most effective principle by far emerged, i.e. the interaction of ultrasonic waves with gas bubbles.

In fact, it was often microscopic gas bubbles which were the cause of ultrasonic contrast effects after injection of solutions such as X-ray contrast media.

Forms		Reference
Solutions	0.5 M sodium citrate 0.2 M calcium gluconate	[51]
Emulsions	Perfluoroctyl bromide	[52]
Suspensions	Iodiparmide microparticle	[53]
Gas microbubbles	Gelifundol, Intralipid, Na-iron III gluconate	[54]
	Galactose-microparticle suspensions	[55, 56]
	Gas filled albumin capsules	[57]
	Emulsions	[81]

Table 33. Potential ultrasound contrast media from various substance classes

In contrast to rigid particles (e.g. crystals, latex spheres, metal dust, rigid inflexible gas capsules) in aqueous medium which reflect or scatter the ultrasound waves, free gas bubbles or gas bubbles with malleable shells are caused to oscillate by ultrasound; they themselves then send out ultrasound signals which can correspond to the transmitted frequency or are integral multiples or fractions of the excitation frequency; the latter are termed harmonics. Evaluation of the ultrasound signals created by the harmonics facilitates the selective and extremely sensitive detection of the gas bubbles administered with the contrast medium. Excitation with higher energies enables the individual gas bubbles to emit very strong signals, independent of the excitation frequency, leading to an exceptionally sensitive detection via “acoustic emission modes”. In such cases detection of individual bubbles is possible, but they dissolve during the process.

Gas bubbles can be generated by shaking solutions, also by cavitation resulting from rapid injection

through narrow cannulas or pumping of a solution from one container into another, and they can be stabilized for a short time in a more or less viscous medium. However, problems could include:

- the creation of a sufficient quantity of small bubbles,
- reproducibility of the process and
- instability of the preparation.

The systematic development of reproducibly manufactured, reliably effective and proven well-tolerated contrast media for ultrasonography has only been going on for the last 15 years. A first preparation (Echovist®, Schering AG) was launched in 1988 and is now approved for echocardiography, phlebography and hysterosalpingo-contrast echography. While Echovist® does not pass the capillaries of the lungs after intravenous injection Levovist® reaches the arterial system. It survives several capillary passages. This is accomplished by coating the gas bubbles with fatty acid for additional stabilization. Levovist® is approved in different ways in different countries for the enhancement of inadequate Doppler signals (e.g. in color Doppler) and B-mode echocardiography. Several other preparations are at varying stages of clinical and experimental testing.

COMPOSITION AND PREPARATION BEFORE USE

Echovist®-300

Echovist®-300 is the first contrast medium approved for ultrasonography. It consists of fine D-galactose particles with a special surface structure, which are loosely aggregated to granules which are visible to the

	20 ml bottle 3 g D-galactose granulate from micro-particles	10 ml bottle 8.5 ml 20% (w/v) D-galactose solution
Suspension		
Micro-particle concentration (dissolution not considered)	300 mg/ml	
Micro-particles, 99%	< 12 µm	
Gas volume (in 10 ml)	75–300 µl	
Mean gas bubble size 97%	3 µm < 7 µm	
Viscosity (25°C, mPa. s)	11.4	
Osmolality of the fresh suspension (mOsm/kg H_2O)	1740	
Total galactose	450 mg/ml	

Table 34. Echovist®: Composition and characteristics of the initial materials and the injection suspension

naked eye. The granulate is available in 3 g portions in a 20 ml bottle. A second bottle contains 8.5 ml of a 20% galactose solution. D-galactose is a simple natural sugar which is found in milk and other foods.

The suspension medium is added to the granulate and vigorously shaken for 5 seconds immediately before use. This causes the granules to dissolve into individual microparticles and creates a ca. 10 ml portion of a white suspension, which contains very fine gas bubbles and the not yet completely dissolved micro-crystals of the galactose (table 34, fig. 29).

In its 20 ml bottle or drawn up into the syringe, the preparation remains fully effective for at least 5 minutes, i.e. the

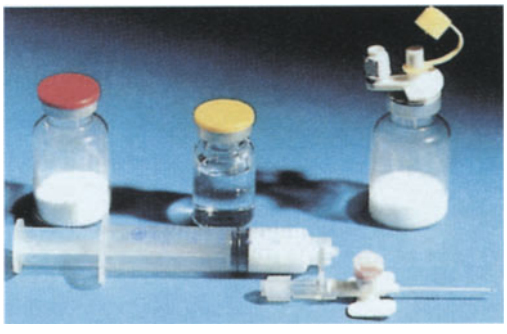


Fig. 29. Echovist®-300; from left to right: 20 ml bottle with granulate; 10 ml bottle with galactose solution; 20 ml bottle with granulate after removal of the protective cap, insertion of the mandrel, addition of the galactose solution and mixing; in the foreground: Echovist in the syringe with injection cannula

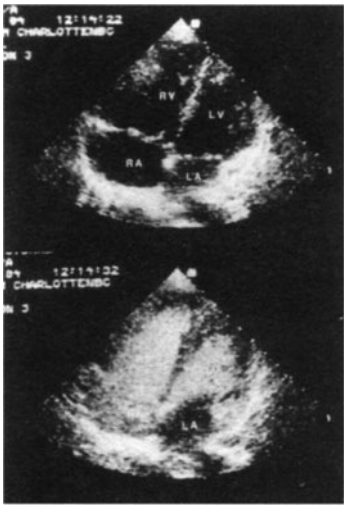


Fig. 30. *Above,* Apical four chamber view of the heart (right ventricle = RV, left atrium and left ventricle before contrast medium administration.) *Below,* After i.v. injection of Echovist®-300, the contrast medium travels with the bloodstream into the right heart. Passage into the left ventricle is only possible due to a defect in the cardiac septum. Echovist® does not enter the left heart via the lungs

bubbles responsible for the effect do not rise or dissolve in the liquid.

However, the prepared suspension is sensitive to

- heat (above room temperature)
- significant pressure changes. In order to avoid under- or overpressure, a wide-lumen mandrel is supplied which can be placed on the granulate bottle.
- Any suspension not used 15 minutes after preparation must be discarded as the echogenic characteristics are diminished.

APPLICATION

Echovist®-300 is approved for right heart disease diagnostics, including septum defects (fig. 30) and the diagnosis of venous diseases.

For adults, 4–10 ml are intravenously injected rapidly through a cannula with a sufficiently wide lumen. The arm must be positioned in such a way that rapid drainage of the contrast medium is possible. If necessary, 10 ml physiological saline solution can, e.g. via a 3-way valve, be injected immediately thereafter in order to facilitate the progress of the contrast medium bolus. A maximum dosage of 10 ml per intravenous injection, and 50 ml in the course of 5 individual injections per patient, is considered to be safe. There is insufficient clinical experience with higher dosages.

Echovist®-200

Echovist®-200 is a less highly concentrated version of Echovist®. It is prepared in the same manner as Echovist®-300. Again 3 g of D-galactose microparticles

Formulation	Microparticle concentration	Total galactose	Viscosity at 25° C	Osmolality
Echovist®-200	200 mg/ml	38%	4 mPa · s	1 700 mosm/kg H_2O
Echovist®-300	300 mg/ml	47%	8 mPa · s	1 740 mosm/kg H_2O

Table 35. Physicochemical properties of Echovist®

are suspended in 13.5 ml of the D-galactose solution supplied (table 35). The preparation is recommended for B-mode echocardiography in children up to the age of 5 and for hysterosalpingocontrast sonography.

The arterial injection of Echovist® (200 mg micro-particle per ml) has been performed under experimental conditions (fig. 31; [58]); there is neither sufficient clinical experience nor is the preparation approved for this application.

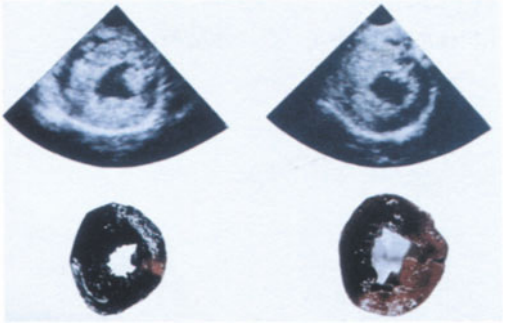


Fig. 31. *Above,* Examination of a dog after injection of Echovist in the aortic arch; the contrast medium enters the ring-shaped myocardium through the coronary arteries. A small infarction zone *(left)* and a large infarction zone *(right)* are bypassed. *Below,* Cuts through the heart after coloration with a vital stain; the infarction zones are not darkened by the stain

Levovist®

By adding small amounts of palmitic acid and altering the manufacturing process it has become possible to prevent the gas bubbles from dissolving and so to extend their lifetime far beyond that of Echovist® (table 36). Although Levovist® and Echovist® differ little in appearance there are some differences in the handling (fig. 32) and considerable differences in the nature of the effect.

Instead of the galactose solution water for injection is used in the preparation. This results in a much lower osmolality and a slightly lower viscosity (table 37). Levovist® is supplied in

D-Galactose	99.9%
Palmitic acid	0.1%
Microparticles	99% < 8 µm
Gas volume in the suspension	< 100 µl/g microparticles
Average gas bubble size	2–4 µm

Table 36. Composition of Levovist®

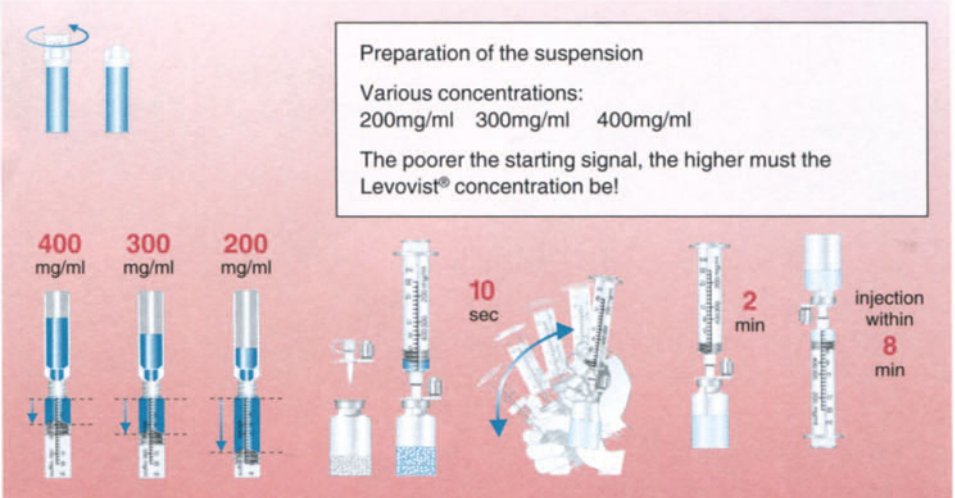


Fig. 32. Levovist® – preparation

Formulation	Total galactose	Viscosity at 25° C	Osmolality
200 mg particles/ml	20%	1.4 mPa · s	910 mosm/kg H_2O
300 mg particles/ml	30%	3.6 mPa · s	980 mosm/kg H_2O
400 mg particles/ml	40%	8.0 mPa · s	950 mosm/kg H_2O

Table 37. Physicochemical properties of Levovist®

Package size	Concentration, microparticles/ml	Water for injection	Total volume
2.5 g	400	5 ml	6.5 ml
	300	7 ml	8.5 ml
	200	11 ml	12.5 ml
4.0 g	400	8 ml	10.5 ml
	300	11 ml	13.5 ml
	200	17 ml	19.5 ml

Table 38. Preparation of the suspension

two dosage forms with 2.5 g or 4 g of granules which allow the user to choose between 3 different concentrations (table 38).

Like all ultrasound contrast media the preparation is somewhat sensitive to pressure, a property which is compensated by the provision of a special wide-bore withdrawal spike. Even the minimally viscous ready-to-use suspension with 200 mg microparticles/ml is stable for 8 minutes without loss of effective-

Fig. 33. Levovist® – materials for infusion

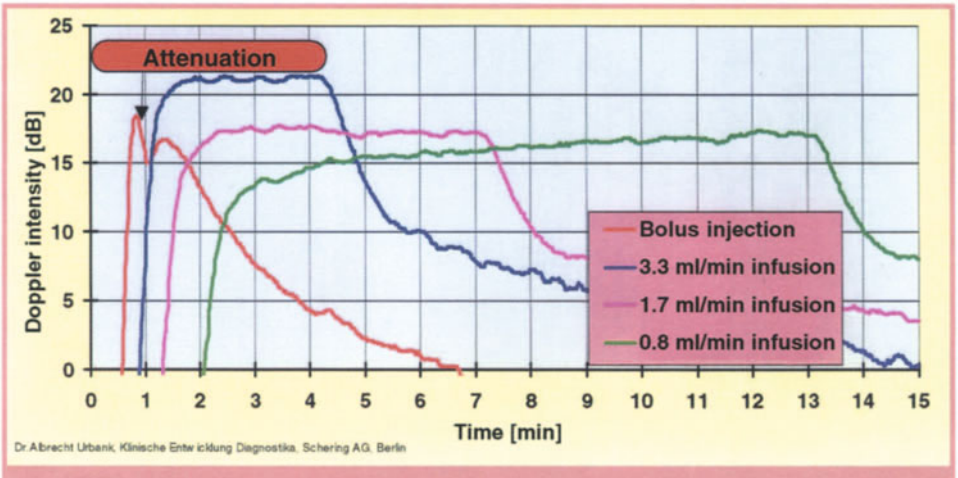


Fig. 34a. In-vitro study of the efficacy of Levovist®, 1 vial, 4 g, 300 mg microparticles/ml, ~ 10 ml volume bolus as compared to infusion at various flow rates

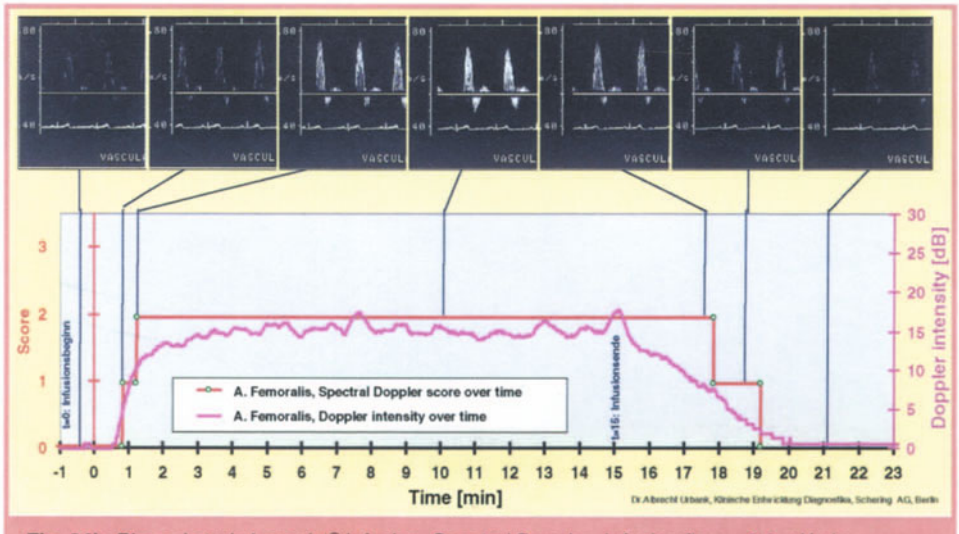


Fig. 34b. Phase I study Levovist® Infusion, Spectral Doppler. Infusion flow = 0.9 ml/min., Levovist® concentration 400 mg/ml, 2 vials of Levovist® à 4 g

ness, while the higher concentrations with 300 or 400 mg particles/ml are stable for 15 minutes and longer.

Following bolus injection marked signal enhancement usually persists for 1–2 minutes. Experience has

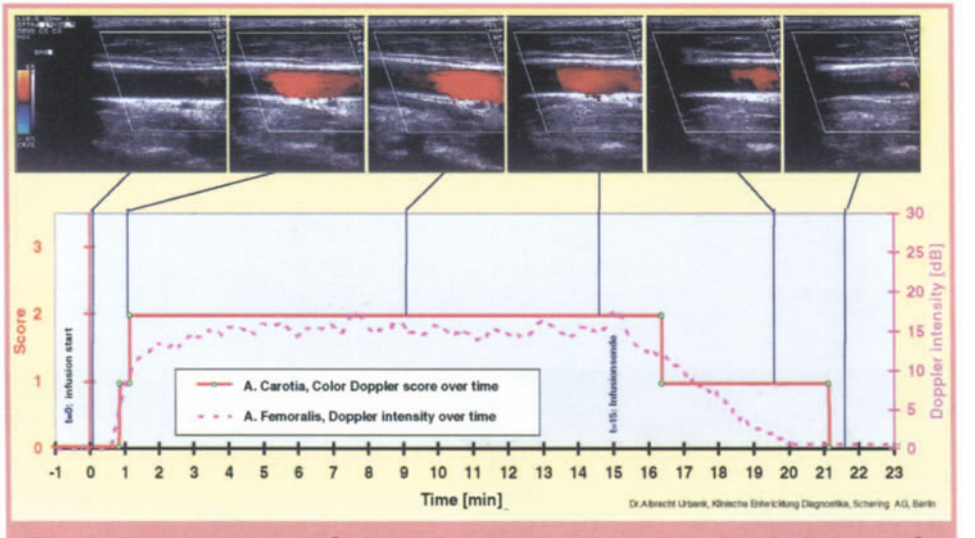


Fig. 34c. Phase I study Levovist® Infusion, Color Doppler. Infusion flow = 0.9 ml/min, Levovist® concentration 400 mg/ml, 2 vials Levovist® à 4 g

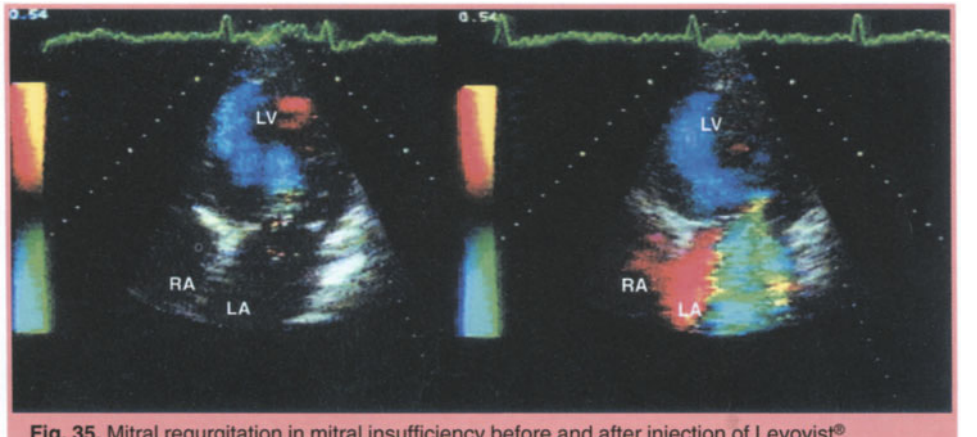


Fig. 35. Mitral regurgitation in mitral insufficiency before and after injection of Levovist®

been gained with up to 6 consecutive injections of a single dose.

In Doppler sonography a prolongation of the effect can be achieved by infusion using e. g. an infusion pump (figs. 33, 34). Only suspensions containing 300 or 400 mg microparticles/ml are suitable for this as they alone are sufficiently stable over the period of handling and infusion due to their somewhat higher viscosity. The recommended infusion rate is 1–2 ml/minute. For infusions of longer duration 2 vials are suspended separately and then drawn up into the same syringe together. The infusion pump manufacturer's instructions and the dimensions of the syringe must always be adhered to.

After intravenous injection Levovist® circulates in the blood, whereby the galactose particles dissolve rapidly, the air bubbles rather more slowly. The bubbles are sufficiently stable to survive the first passage through the lungs and several subsequent capillary passages. This leads to enhancement of the signals in B-mode, primarily in the lumen of the heart, and to enhancement of the Doppler signals in the entire circulatory system (figs. 35, 36). More specific and more sensitive methods of measuring with ultrasonic devices also increasingly permit the recognition of the contrast medium in the parenchyma of the organs or in the tissues irrespective of the presence of macroscopically discernible vessels. This facilitates the detection of hypoperfusion or hyperperfusion, e. g. in the myocardium or in tumors (fig. 37). Levovist®

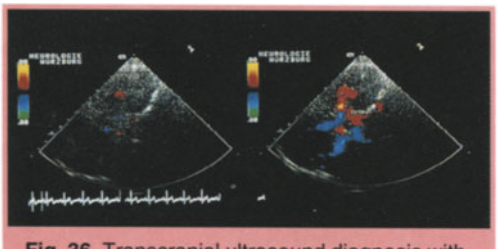


Fig. 36. Transcranial ultrasound diagnosis with Levovist® – complete image of the circulus villisii after administration of the echo contrast medium

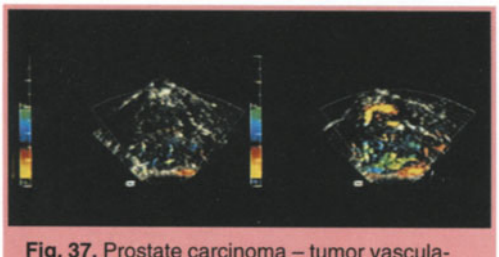


Fig. 37. Prostate carcinoma – tumor vascularization: only after administration of Levovist® is the highly vascularized portion of this prostate carcinoma visible

is particularly suitable for application in the harmonic mode.

Ultrasound contrast media are suitable for the amplification of Doppler signals. This can be especially useful with insufficient flow, lack of accessibility to the region being measured (great depth in tissue, transcranial ultrasound) or lack of scattering elements (erythrocytes). With Echovist®, flow signals were received using the color Doppler technique, e.g. in echocardiography and during irrigation of the tubes [56]. After intravenous administration echo contrast media which are capable of passing the pulmonary capillaries can lead to an increase in the flow signals from a multitude of blood vessels and organs.

PHARMACEUTICAL PRODUCT QUALITY

The industrial production of echo contrast media requires completely new technologies. There is no previous experience with the production and stabilization

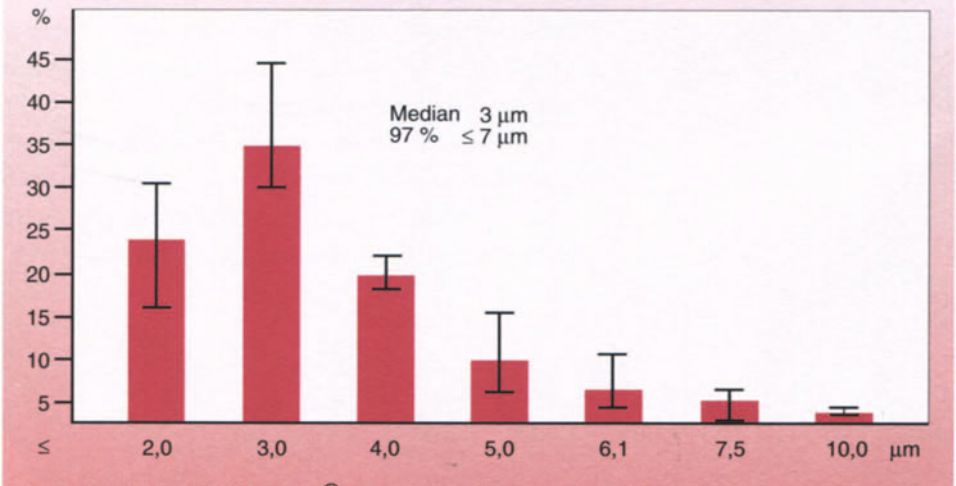


Fig. 38. Bubble size of Echovist® (n = 130.980)

of the finest gas bubbles from any other type of pharmaceutical production. The same applies to the quality control of the temporarily stable preparation ready for injection as well as the experimental testing of its tolerance.

Echovist® and Levovist® consist mainly of chemically pure α-D(+)-galactose. The release of large numbers of gas bubbles of a certain size (fig. 38) during the suspension process is guaranteed by specific physical characteristics of the surface of the microparticles. At the same time, the microparticles may not exceed a certain size so that they do not cause an embolism, and they must not adhere to one another too strongly.

The required characteristics are achieved through a complicated, many-staged production process. In order to guarantee the chemical purity, sterility and exclusion of pyrogens from the galactose, the entire production process must be performed under sterile conditions. The quality of the actual contrasting principle – the gas bubble in the suspension – is determined by the galactose microparticles. Handling of the preparation by the user can only decrease the efficacy of the preparation, not create or improve it, as was the case with previous hand-mixed preparations.

Other echo contrast media currently being developed also use difficult production methods. In addition, the chemical composition and the stability of the delivered form of some preparations can cause problems.

INFLUENCE ON LABORATORY TESTS

Echovist®-300 and Levovist® contain galactose in a dosage up to 4.7 g per 10 ml prepared suspension. Correspondingly, the serum level of galactose is significantly increased by the injection of these products. Measurement of the serum galactose level, e.g. during a hepatic function test can be temporarily disturbed. This effect disappears completely after ca. 24 hours, even with significantly reduced hepatic function.

Other echo contrast media with other compositions could show completely different influences on laboratory tests.

INTERACTIONS WITH MEDICATIONS

There are no known interactions between Echovist® or Levovist® and other drugs or contrast media.

Echo contrast agents are carefully stabilized preparations of very fine gas bubbles. Mixing with medications, injection or infusion solutions should be avoided as nothing is known about the contrast performance and the tolerance of such combinations.

RISKS RELATED TO THE USE OF ECHO CONTRAST MEDIA

Two different aspects must be considered when estimating the risks of using contrast media for ultrasonic diagnostics:

- Risks through gas bubbles or particles.
- Risks through different substances in the preparations.

Side-effects resulting from the injection of particular components can be caused by the embolization of fine blood vessels. This is prevented by the fact that the particles are made as small as possible (< 10 µm) and the high solubility of these particles in the bloodstream and other body fluids. Gas bubbles have the advantage of great efficacy as an ultrasonic contrast medium. Therefore, the use of very small dosages is effective: even 0.1 ml air distributed in many millions of gas bubbles is sufficient to make several liters of blood echogenic. Various echo contrast media containing gas bubbles have been investigated thoroughly for possible embolism risks in both experimental animal and clinical trials. Experience has shown that they are very well tolerated [54, 55, 57].

Emulsions and suspensions of fluids or solids not containing gas bubbles require such high dosages in order to achieve sufficient contrast that the potential for side-effects is much higher.

Echo contrast media based on gas bubbles which have been clinically investigated contain very different substances to produce or stabilize the bubbles. These are natural or nearly natural substances with which much clinical experience has been collected as they are found in other pharmaceutical preparations. Risk evaluation must be performed for each substance and each preparation separately.

Echovist® and Levovist® have been proven to have good tolerance. This also applies to patients with septal defects, in which a significant portion of the contrast medium enters the left heart directly.

Side-effects include thermal sensations, in some cases pain at the injection site, which can be explained by the higher osmolality of Echovist®. Perivascular injection could also be painful for the same reason.

A series of other side-effects, such as dizziness, tingling, numbness and taste sensations were rare, temporary, and required no therapeutic measures.

Echovist® and Levovist® contain galactose. Galactose is contraindicated in patients with galactosemia. Side-effects due to galactose are unknown in other patients. Galactose can be metabolized or renally eliminated. The half-life is less than 10 minutes in patients with normal liver function.

FURTHER DEVELOPMENT OF CONTRAST MEDIA

The development of CM takes place by large under the aspect of further improvement of tolerance and the opening-up of new diagnostic possibilities by means of different pharmacokinetics. In this connection, new technical developments also influence the use of and need for CM with special properties (table 39).

It is expected that modern, established radiological techniques will be developed further with a slight shift of emphasis. The standard radiological method will retain its great importance and will be extended by digital data and image processing. A further increase in the range of cardiac and angiographic diagnostic agents is anticipated for methods requiring CM injection in the future as well. Nonionic CM which are painless in arteriography but which are also safe after intravenous administration will find widespread use. The development of new ionic CM is no longer expected unless they display specific pharmacokinetic or diagnostic properties.

A focus of interest is the search for a liver-specific contrast agent for computer tomography [25, 26, 82, 83, 84]. A sensitive identification of tumors or metastases has a considerable influence on decisions pertaining to the therapy. An image persisting over a fairly prolonged period would assist interventional measures. Clinical trials are ongoing with a preparation for interstitial lymphography. The progress of CT angiography has reopened discussions about the

Increasing the diagnostic possibilities by		
contrast media with improved tolerance	new contrast media with different pharmacokinetics/ distribution	new technical developments
more comprehensive and exact description of the morphology, better function diagnosis		

Table 39. Development of contrast media

search for contrast media which can remain in the blood for long periods.

New approaches in X-ray contrast media research have evolved from studies with metal ion chelates for magnetic resonance imaging [85]. The heavy elements absorb X-rays rather more effectively than iodine but are much more difficult to bind to organic, well tolerated and excretable substances in a suitable form. Initial clinical applications do, however, demonstrate the suitability of chelates for X-ray techniques [86, 87].

New technical developments will further extend and modify the diagnostic possibilities in the years to come. Dynamic, physiologically controlled and high-resolution scanners can be expected to improve the clarity of detail in CT; scanners with very short scanning times are currently being introduced into clinical practice. With the rapid infusion of well-tolerated CM even better information can be provided about tissue perfusion.

In addition to the existing products a number of echo-enhancing agents are being tested for improved detection of blood vessels and tissue perfusion [26, 55–57, 88, 89, 90].

The diagnostic properties of most preparations appear, in terms of the current state of knowledge, to be very similar. Specifically binding and drug-releasing sonographic contrast media are in the very early stages of research. Just as important as the development of new pharmaceutical preparations is the assimilation of the ultrasonic equipment to the properties of the microbubbles used as contrasting agents; the sensitivity of detection can be multiplied many times by using the altered frequencies generated by the bubbles after excitation with ultrasound. In this way, the potential applications of even those prepara-

tions already on the market can be continuously extended.

The benefit of contrast agents in magnetic resonance imaging has been unequivocally proved. The intravenous or oral administration of paramagnetic substances leads to considerable enhancement of the intensity of the signals emitted from certain parts of the organism. It is possible to enhance the contrast in the GI tract, the kidneys and urinary tract, in areas of blood-brain barrier breakdown and in inflammations, tumors and infarcts [27]. In MR also CM with a different specificity are under development [61].

In MR angiography contrast media reduce the dependence of the method on flow and permit the use of quicker sequences with better spatial resolution. Superior liver-specific contrast media are at an advanced stage of clinical testing. Metastases can be distinguished from lymph node tissue on intravenous injection of magnetites. Still earlier development projects concentrate on gadolinium-containing agents for the intravascular spaces and for the precise differentiation of tumors and benign lesions or on agents for detecting necrotic tissue after infarcts or therapeutic intervention [91]. Due to their high degree of efficacy the paramagnetic contrast agents occupy a middle position between the X-ray contrast media and the radiopharmaceuticals. Compared to the still much lower-dosed radiopharmaceuticals they profit from the good spatial and temporal resolution of modern MR equipment and its high contrast sensitivity.

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COMMERCIAL BRANDS AND THEIR RESPECTIVE IODINE CONTENT (G)

1.1 Uro-angiographic agents, nonionic

Ultravist	150	240	300	370
Iodine concentr. (mg/ml)	150	240	300	370
Iodine content (g) in Ampoule 5 ml	—	—	1.5	—
Vial 10 ml	—	—	3.0	—
Vial 20 ml	—	—	6.0	—
Vial 30 ml	—	—	—	11.1
Bottle 50 ml	7.5	12.0	15.0	18.5
Bottle 75 ml	—	—	22.5	—
Bottle 100 ml	—	—	30.0	37.0
Bottle 150 ml	—	—	45.0	—
Bottle 200 ml	—	—	60.0	74.0
Bottle 500 ml	—	—	150.0	—

1.2 Uro-angiographic agents, ionic

Angiografin		
Iodide concentr. (mg/ml)		306
Iodine content (g) in Bottle 50 ml		15.3
Bottle 100 ml		30.6

Urografin	30%	60%	76%
Iodide concentr. (mg/ml)	146	292	370
Iodine content (g) in Ampoule 20 ml	—	5.84	7.4
Bottle 50 ml	—	—	18.4
Bottle 100 ml	—	—	37.0
Bottle 200 ml	—	—	74.0
Bottle 250 ml	36.5	—	—

Urovision	Urovison for infusions	Urovison R for infusions
Iodine concentr. (mg/ml)	168	168
Ampoule 10 ml	—	1.68
Bottle 100 ml	—	16.8
Bottle 125 ml	—	21
Bottle 250 ml	42	42

Iodine content (g) in

	Urovist	Urovist for infusions	Urovist for infusions 30%
Iodine concentration (mg/ml)	306	306	141
Ampoule 30 ml	9.18	—	—
Bottle 100 ml	—	30.25	—
Bottle 250 ml	—	—	35.3

Iodine content (g) in

2. Myelography and other body cavities, nonionic

Isovist		
Iodine concentr. (mg/ml)	240	300
Ampoule 5 ml	—	1.5
Vial 10 ml	2.4	3.0
Vial 20 ml	4.8	—

Iodine content (g) in

3.1 Cholegraphic agents, i.v.

	Biliscopin	Biliscopin short infusion	Biliscopin for infusion
Iodine concentr. (mg/ml)	180	108	50
Ampoule 30 ml	5.4	—	—
Bottle 50 ml	—	4.5	—
Bottle 100 ml	—	—	5.0

Iodine content (g) in

	Iodine content (g) in
3.2 Cholegraphic agents, oral	
Biloptin	
6 Capsules	1.8
12 Capsules	3.7

	Iodine content (g) in
4. Contrast media for the gastro-intestinal tract	
Gastrografin	
Iodine concentr. (mg/ml)	370
Bottle 100 ml	37

	Contrast media content (g) in
5. Contrast media for magnetic resonance imaging	
Magnevist	
Contrast medium concentr. (mg/ml)	469
Vial 5 ml	2.4
Vial 10 ml	4.7
Vial 15 ml	7.0
Vial 20 ml	9.4
Vial 30 ml	14.1
Vial 100 ml	46.9
Magnevist enteral	
Contrast medium concentr. (mg/ml)	9.39
Bottle 100 ml	0.938

6. Contrast media for sonographic imaging

Echovist 200

Vial 15 ml	13.5 ml	galactose solution
Vial 20 ml	3 g	galactose-granulate

Echovist 300

Vial 10 ml	8.5 ml	galactose solution
Vial 20 ml	3 g	galactose-granulate

Levovist

Vial 20 ml	2.5 g	galactose-palmitic acid-granulate
Vial 20 ml	4 g	galactose-palmitic acid-granulate